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UA team's tobacco snags methamphetamine in blood

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ARKANSAS DEMOCRAT-GAZETTE

In 1571, the Spanish doctor Nicholas Monardes wrote about the medicinal virtues of tobacco, recently discovered in America.

According to the doctor, tobacco cured 36 maladies, including toothache, chilblain, worms and stomach ache. It was particularly good at healing "griefs of the head."

Nowadays, many people learn about the health effects of tobacco from a different doctor, the U.S. surgeon general. But a group of University of Arkansas researchers are talking up tobacco again, saying it could quell the problems caused by PCP and methamphetamine.

Using mouse genes, the UA researchers have engineered an antibody-producing tobacco plant that neutralizes methamphetamine and PCP. The antibodies could mitigate psychotic episodes in overdosing patients, safeguard fetuses against prenatal exposures and make rehabilitation a lot easier on addicts, researchers said.

"Imagine something on board in your body ready to catch the methamphetamine when it got in," said Ralph Henry, a UA-Fayetteville biology professor who rears the genetically-altered tobacco. "If you fell off the wagon, you'd get no reward for that."

The researchers, divided between the Fayetteville campus and University of Arkansas for Medical Sciences in Little Rock, have founded a pharmaceutical start-up company as they seek permission to begin clinical trials from the Food and Drug Administration.

But Frank Vocci, the drug treatment director at the federal drug czar's office, remains cautious. Antibody therapies are not a cure-all for drug addiction, and ethical difficulties of consent remain as the researchers seek to test and administer the agri-medicine, he said.

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Ralph Henry, a biology professor at the University of Arkansas at Fayetteville, shows some of the tobacco plants that are genetically engineered to produce antibodies to counteract the effects of drugs like methamphetamine and PCP.

MOUSY TOBACCO

Antibodies are the natural disease fighters in blood. They're created, for instance, after a measles vaccination or a bout of chicken pox. Usually, the antibody binds to the virus or bacterium and acts as a signal so that destroyer cells can recognize and eat the invading body.

But with PCP and methamphetamine, the antibody works by itself. The large antibody latches onto the tiny drug molecule, which is then too big to cross a membrane into the brain. The liver filters the drug out of the blood; the addict never feels the euphoria of the drug acting on the brain, researchers said.

Using plants as antibody factories is new. But the concept of plant-based medicine is not, said UAMS pharmacology professor S. Michael Owens, the lead researcher in the project and the patent holder on amphetamine-fighting antibodies.

"You go back thousands of years, and medicine would be extracting a crude plant product. Someone would grind up some leaves, put it in some water and make you drink it," he said.

Plants don't naturally make antibodies. The Arkansas researchers had to first get an animal to make PCP and methamphetamine antibodies, then engineer the tobacco to do the same.

Pharmaceutical companies have used animals to make antibodies for decades, Owens said. Horses, for instance, are given dosages of snake venom. They react by building up antibodies in their blood, which is then filtered commercially for antivenin.

So Owens began by giving PCP and methamphetamine to mice and isolating the spleen cells that responded with antibodies. He fused spleen cells to cancer cells, which properly fed, keep dividing forever. Then it was just a matter of growing cells in a petri dish — or large-scale, commercial bioreactors — and collecting the secreted antibodies.

But making antibodies this way is expensive. Big bioreactors can cost hundreds of millions of dollars, Henry said.

On the other hand, a crop of genetically engineered tobacco plants is low maintenance and easy to scale back or ramp up on demand. Overall, the plant method is between two and five times cheaper than producing antibodies in bioreactors, Henry said.

Henry estimates that he needs 200 square feet of tobacco to produce a single human dose. Total production costs would be about $200.

That's far less than existing antibody therapies, which for cancer treatments can cost as much as $2,000.

Owens faced a second issue. Antibodies made from human rather than mouse cells are safer, since the body sometimes has an allergic reaction to foreign antibodies and goes into anaphylactic shock. But there is no easy way to get humans to make drug antibodies, Owens said.

"It wouldn't be ethical to immunize you for meth and take your spleen out," he said.

Owens already had pinpointed the mouse genes for the antibodies. He isolated the essential portion of the mouse gene: the DNA for the part of the antibody that latches onto the drugs. He combined this gene material with safer human DNA and created what's known as a chimeric gene — a gene of antibody instructions that is part man, part mouse.

Owens figures the chimeric gene will produce safer antibodies than a full-fledged mouse gene.

It's Henry's job to get the genes to do the same thing in tobacco that they do in mouse spleens. He injects the genes into bits of tobacco leaf. Using plant hormones, he coaxes the tobacco cells to root and grow under fluorescent light in a temperature-controlled room.

Some plants are more potent than others. A research assistant in Henry's lab breaks open the flowering seed pods and bottles the tiny seed beads by family and generation. Only the best strains will be used in a new greenhouse Henry plans on stocking this summer.

A post-doctoral student works on extraction techniques with a variety of fancy centrifuges and filtering tools. The brute-force method of the blender works, but Henry says it's better to soak the tobacco leaves, then spin and extract the yellow-tinged antibody fluid.

A test tube containing dried and filtered antibodies looks similar to PCP, Henry said. The antibodies, which are proteins, contain none of the nicotine or carcinogens associated with tobacco.

Owens, along with UAMS researchers Brooks Gentry and Donald McMillan, began testing the antibodies on rats.

Rats given PCP and methamphetamine scurry around frantically. On drugs, the rats can travel up to half a mile in a day, Owens said. But when given the antibodies, that distance is reduced to 50 yards, the daily distance traveled by a normal rat.

"In four minutes, it's sitting in a corner cleaning itself, starting to get a little bored. In other words, the therapy works," Henry said.

The scientists think the therapy neutralizes the physical effects of the drug. But the therapy won't necessarily stop the addiction or psychological craving for the drug, Henry said.

Yet even so, another rat experiment offers hope that, without the reward of physical pleasure, addictions wane. In the experiment, rats are taught to give themselves methamphetamine and PCP whenever they feel like it. But under high doses of the antibodies, the rats eventually lose interest in self-medicating, Owens said.

ACTIVE VERSUS PASSIVE

The therapies are promising but not a panacea, said Vocci, the treatment research director at the National Institute on Drug Abuse, the research arm of the drug czar's office.

Addicts who realize a high is impossible with the therapy may find a new drug to use, Vocci said.

But Vocci thinks antibody therapies could be an improvement over drug substitutes.

The advantage of antibody therapies is that they keep the drugs from reaching the brain altogether, he said. The therapies can be divided into two classes: passive and active.

The UA researchers are preparing passive antibodies that are injected directly into the bloodstream and eventually disappear. In the active approach, the body is vaccinated so that it makes its own antibodies in perpetuity.

Passive antibodies are more expensive but work quickly. Active approaches could provide a lasting immunity but work more sluggishly. Scientists already have begun clinical trials for a nicotine vaccine, and a cocaine vaccine also is in the works, Vocci said.

The first PCP-antibody tests on humans are still about two years away, Owens said.

The FDA requires a pharmaceutical company to sponsor a new drug entering clinical trials. But most big pharmaceutical companies weren't interested in the antibody therapies, since it affected a small population with a limited ability to pay, Henry said.

"It's not a multibillion-dollar drug we're talking about. It's not aspirin," Henry said.

So in February, the researchers set up Inflection Therapeutics, which will operate out of the UAMS BioVentures incubator.

The National Institute on Drug Abuse gave the researchers $5.5 million in 2001. Inflection Therapeutics is seeking another $1.5 million from the institute, specifically to begin trials for the PCP antibodies. The researchers also get money from the Arkansas Bioscience Institute, which in turn is funded by Arkansas' share of the 1998 settlement with tobacco companies.

Henry notes the irony of tobacco money resulting in a new use for tobacco. "We've come full circle," he said.

ETHICAL QUESTIONS

The benefits of the UA research could be substantial if all the costs of fighting drug abuse are considered, said Henrick Harwood, an economist and consultant with the Washington-based Lewin group.

Harwood estimates the annual cost of drug addiction at $145 billion. That includes the costs of crime, lost productivity and health costs. It also includes approximately $8 billion that's spent on fighting drug addiction, he said.

Drug addiction costs an individual tens of thousands of dollars per year, Harwood said. So even if a round of antibody therapy costs $1,000 — but it kept a user off drugs for six to nine months — its benefits outweigh its costs, he said.

Harwood also chaired a National Academy of Sciences study that examined the ethical considerations in antibody therapies.

Many of the ethical problems are in finding people to test the therapy on. You can't dose volunteers with an illegal drug. And many of the patients that enter in an overdose situation would not be lucid enough to give consent, Harwood said.

But other ethical concerns will arise after a viable therapy is developed, Harwood said. He worries that the legal system might view the therapies as a cure-all.

"This might seem to judges, to prison managers and to family welfare authorities to be such an effective therapy and be so important, they would try and mandate and force a person to get it," he said.