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**HEADLINE:** Can an Antibody Gobble Up Cocaine Cravings?

**BYLINE:** Guy **Gugliotta,** Washington Post Staff Writer

**BODY:**
Biochemist Donald W. Landry took up the cocaine challenge at the height of the crack epidemic, after he heard then-President George Bush ask in a speech whether science might be able to devise a vaccine that could somehow render addictive drugs harmless.

A decade later, he may have done it. Using methods seldom applied in drug abuse research, he built a "catalytic antibody" that eats cocaine in a lab rat's bloodstream the way Pac-Man gobbles bad guys in a computer maze.

And this spring, the Gaithersburg biotech company MedImmune Inc. will join forces with him to refine his technique to make an antibody strong enough to treat cocaine abuse in humans.

Landry may not have found the "magic bullet" in the war on drugs, but he appears to be as close as anyone. "If he is successful," said Frank Vocci, director of treatment research and development at the National Institute on Drug Abuse, "he would actually have an antibody able to reduce cocaine to an inactive substance as fast as people put it into their bodies."

Success is by no means assured. Scott Koenig, MedImmune's senior vice president for research, said that while Landry "has shown conceptually that it can work," the antibody does not yet function rapidly or efficiently enough to be used in humans.

Koenig said that MedImmune, by engineering and testing thousands of variants of Landry's antibody, as well as new candidates, expects to show whether the technique can be commercially viable.

"We have no way of knowing," Koenig said. "But we'll have an answer in 2000." Once proven, however, the treatment would still require some years of clinical evaluation before it could reach the market, he said.

The potential is enormous. The President's Office of National Drug Control Policy (ONDCP), which has given Landry $ 2.8 million in research grants since 1994, estimates that there are 5.2 million users of cocaine and its derivatives in the United States, and 3.3 million addicts.

Americans spend $ 39 billion per year on cocaine, and cocaine's "social cost" in law enforcement, prisons, rehabilitation, lost wages, medical care and family violence is another $ 66 billion, ONDCP estimates.

Landry's--and MedImmune's--goal is to create an antibody that will mop up any cocaine that might be in a person's bloodstream for about a month. Add boosters so the person goes four or five months without a reinforcing high, and the craving goes away.

"And when that happens, rates of abstinence go way up," Landry said, citing studies he said showed that heroin treatment with both methadone and counseling produced abstinence rates of 60 percent to 80 percent, compared with 10 percent to 30 percent for programs relying on counseling alone.

Still, he cautioned, while the antibody effectively "vaccinates" a person against cocaine for a month, it is not a "vaccine" that causes a person's body to become permanently immune.

Also, "a vaccine is different for something you want than for something you don't want," said Alan I. Leshner, director of the National Institute on Drug Abuse. "People want cocaine," and they can always wait for the vaccine to wear off.

When Landry, a biochemist at the Columbia University College of Physicians and Surgeons in New York, began his research, the development of catalytic antibodies was in its infancy.

Unlike natural antibodies, which are formed within the human body and neutralize foreign substances by binding to them, a catalytic antibody is created artificially in the lab and injected into the bloodstream.

Outside the host, scientists are able to engineer the antibody so that it will not only bind to a foreign substance, but will encourage, or "catalyze," a chemical reaction that will cause the substance to break up.

Cocaine is a particularly good target for such a technique, Landry explained, because its molecules could be cleaved easily to produce two harmless chemicals. A catalytic antibody that encouraged this cleavage reaction would, in effect, kill cocaine.

First, Landry's team built a synthetic "analogue" that mimicked the molecular structure of cocaine as it breaks apart. They injected it as a foreign substance into lab mice, which created natural antibodies to counter it.

Then they removed the mice's spleens, isolated the cells that produced the antibodies and cultured them individually. Some of the cells produced catalytic antibodies that would, in theory, search out cocaine molecules, induce them to change chemically and break apart, then move on in search of a new binding partner--the Pac-Man effect.

This suggested that unlike conventional vaccines, which could be overwhelmed by an abuser who exhausts the supply of antibodies by taking more and more cocaine, the catalytic antibody binds and kills again and again. "It is not one-to-one," Landry said.

For this reason, although some conventional cocaine vaccines have reached clinical trials, they can all be surmounted, Vocci said. These will likely be used to blunt the initial "rush" when an abstainer falls off the wagon.

Landry's initial report on his research in 1993 suggested that the antibodies would not only repeatedly bind and neutralize cocaine, but theoretically could do it so fast that the cocaine would be broken up before it reached the brain.

This was a marked difference from the battle plan embodied in methadone and other "blockers" that screen a drug's effects by cementing themselves to the same pleasure receptors in the brain that the drug stimulates. Instead, Landry's antibodies would intercept the cocaine before it could get into these neurological pathways.

In 1998, he showed that this was possible. In the first "overdose" experiment, Landry's team injected rats with lab-created catalytic antibodies, then gave them enough cocaine to kill them. The rats didn't die.

In the second "addiction" experiment, the team trained rats to push a lever to receive a dose of cocaine. When salt water was substituted, the rats pushed the lever a few times, but soon lost interest.

Then the team injected the rats with antibodies and tried to dose them with cocaine again. The rats tried the mixture, then ignored it, as if it were salt water.

Nevertheless, Landry said, "everything we've accomplished so far is merely proof of principle." Indeed, both Landry and MedImmune agree that Landry's best-performing antibody binds to individual molecules much too sluggishly and doesn't change targets fast enough.

The antibody also probably needs to be "humanized," so a patient's body will not attack it by making an antibody for the antibody. MedImmune will try to do all this by testing many sample antibodies--both Landry's and others made by MedImmune--and "tweaking" them to enhance performance.

"I don't want to say it's a no-brainer," said MedImmune's Koenig. "It's challenging, but we have the experience to give it a good shot. If it can be done, we'll do it."

A proposal for treating addiction: Introduce into the bloodstream antibodies that chop up cocaine molecules before they reach the brain.

**GRAPHIC:** ILL,,TOMO NARASHIMA