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On a biting cold February evening in central Arkansas, the Lonoke County Sheriff's Office is busy preparing to bust a local drug dealer for selling methamphetamine. Lieutenant Jim Kulesa sits at his desk counting out \$20 bills, reminding his team to make sure to crumple them up so that the money looks less suspiciously fresh when they use it for the transaction, which police refer to as a 'controlled buy'. It's 6 p.m. and the office reeks of skunky marijuana, recently seized.

Kulesa checks his team's paperwork authorizing the buy. "Controlled purchase?" he says in an affected voice, shooting a glance at a younger officer. "You getting fancy on me?"

Kulesa says that when he busts users and dealers they sometimes plead sickness. "They tell me 'I need help—I want to go to rehab,' and I say, 'Well, they have a good rehab program in prison.'" But soon after many addicts get out of jail, they are arrested on new charges, making the task of busting people for methamphetamine seem endless.

Methamphetamine, or 'meth', has remained the drug of choice for rural users for more than a decade. It is cheap and was—until recently—easy to cook up out of readily obtainable ingredients. New restrictions have made it harder to buy raw ingredients, but, in Lonoke, deer hunters still stumble over remote backwoods 'labs' where criminals cook up meth.

Lonoke is a low, flat county where many people farm rice, soy or fish. Other residents have jobs at the gun factory or commute to the state capital, Little Rock, for work. At the local pharmacy, Ray Lackie, a heavysset man with silver hair, has been filling prescriptions since 1965. Ten or fifteen years have passed since the nervous, scruffy characters with bad teeth started showing up at the store and asking for cold medicines containing pseudoephedrine or, more recently, iodine—both ingredients used for making meth. But Lackie no longer stocks either type of product. "I could have 'em lined up outside the door if I did," he says.

A hit of meth will flood the brain with the reward-signaling compound dopamine. As a chemical cousin to amphetamine, meth keeps you up and makes you feel great—at first. It is highly addictive and, for many users, soon subsumes everything else in their lives: work, children, hygiene. Long-term use can lead to psychosis and can rot the teeth to blackened nubs.

For the roughly 700,000 daily meth users in the US, including those that Kulesa's team might bust tonight, there are no pharmaceutical treatment options whatsoever to help them overcome their addiction. Addicts struggling to go clean have to do it on sheer willpower and talk therapy.

Twenty miles east of Lonoke, at the University of Arkansas for Medical Sciences in Little Rock, a researcher named Michael Owens is trying to change this situation. If his hopes for new addiction therapies materialize, Kulesa and his team may someday be able to do something besides bust one meth user after another on an

IMMUNE to the HIGH

Current medications used to treat drug addiction help to some extent by easing withdrawal symptoms, but these treatments cannot curb the high that people receive when they relapse and take a hit of the drug. **Emma Marris** explores how researchers are working on a way to make these tempting drug highs history for recovering addicts.

unending merry-go-round. Owens is developing treatments to have the opposite function of meth: they will prevent and stop the drug high. And they will do so using the addict's own immune system. Someday, Owens hopes, the products of a meth lab and his lab will meet in a user's veins—and that person will feel nothing.

Search and destroy

When foreign particles enter the bloodstream, the immune system kicks into high gear and clears them away. But most drugs of abuse are simply too small to be recognized and destroyed by an untrained immune system. They are sleek little molecules that fly quickly from the pipe or syringe to receptors in the brain, slipping through blood-organ barriers and under the noses of big, lumbering immune cells. The goal of vaccines is to train the immune system to recognize a drug and create enough circulating antibodies to bind and thereby disable incoming drug molecules.

The idea of using the immune system to battle drug addiction was first explored in 1974, when a team at the University of Chicago found that by injecting a rhesus monkey with a morphine-based compound, they could decrease the monkey's interest in self-administering heroin¹.

Owens fell into working on immunological approaches to fighting addiction because of an adviser's project on phencyclidine, better known as PCP. In 1985, they succeeded in stimulating goats to produce antibodies with a high affinity for binding the drug, neutralizing its mind-altering effects². Owens stayed in the field because he was interested in the technical challenge and because he felt he'd found a



Christopher Furlong

Futile fix: Vaccines work to stop the rush from smoking, but only in some people.

promising niche in biomedicine where he could make a name for himself. But along the way, he has developed a great deal of sympathy for drug addicts and their families, who routinely call him at his office in desperation, asking for a cure. "They want to know if they can have it right now," he says. "They'll drive right down."

Owens's work in the 1980s helped revived interest in the field, and there are now several academic labs and small companies investigating immunological approaches to treat drug addiction.

Still, research has moved slowly, partly owing to difficult technical challenges and—some in the field say—the attitude in the United States toward drug addiction, which many people still view as a moral failing. "Part of the problem when developing pharmacology for drugs of addiction is that it takes a lot of money, and so it requires the participation of big pharma," says Kathleen Kantak, a behavioral neuroscientist at Boston University. "But they want to keep their names clear of that because of the perception that this is a character flaw rather than a brain disease."

Nevertheless, a few vaccines are in development. Although most potential vaccines remain in the animal-testing phase, a handful of human trials involving nicotine and cocaine vaccines have already finished or are in progress. Researchers view nicotine as a promising target because of the huge market for antismoking agents: more than 1 billion people smoke worldwide, and, of those living in industrialized nations, 70% want to quit^{3,4}.

Last year, the Swiss pharmaceutical giant Novartis acquired a nicotine vaccine from a smaller biotech company. And the US Food and Drug Administration (FDA) recently granted fast-track status to one potential vaccine, NicVAX, owned by the Rockville, Maryland-based company Nabi Biopharmaceuticals. So far, only 30% of smokers taking NicVax in trials developed a sufficient number of antibodies to make a difference in their habits. The mixed results point to what is perhaps the largest hurdle for vaccines: human variation.



Emma Marriss

Prescription for change: Some pharmacies have stopped stocking medications used to make meth.

A standard dose of a vaccine will produce very different responses in different people, for reasons that are still not well understood.

The Bermuda-based firm Celtic Pharma is currently coordinating a trial with more than 500 participants for its own nicotine vaccine, TA-NIC. But it also has hopes for another vaccine it owns, called TA-CD, which targets cocaine. An early-stage trial of TA-CD, run by Margaret Haney of Columbia University in New York, tracked antibody production in a small number of cocaine users for 13 weeks. The subjects received various regimens and doses of the vaccine, and the jabs clearly worked for some of them, who “complained bitterly” that smoking crack cocaine wasn’t doing the trick for them anymore. The preliminary results encouraged Haney. “I’ve never seen any medication produce such a strong blunting of response,” she says. However, as with other vaccines, antibody production varied from person to person.

“My guess,” says Kantak, “and it’s just my own guess, is that even though the cocaine vaccine is a lot further along than the nicotine vaccine, the FDA might go forward with the nicotine vaccine first, because it is less controversial.”

The death of meth?

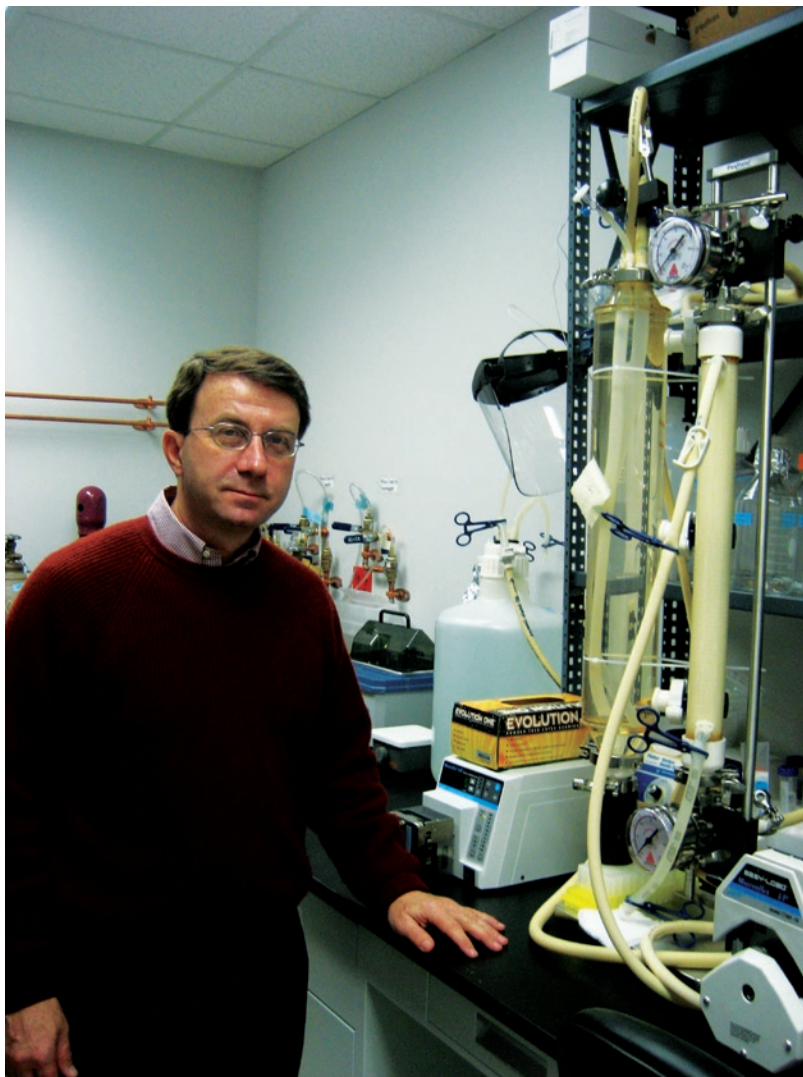
Owens heads one of only a few labs focusing on treatments for methamphetamine addiction, and he’s still at least a few years from any trials in humans.

Owens has spent decades studying addictive compounds. His own pleasures are less dangerous: gardening and golf. A South Carolina native with neatly parted hair and glasses, and with an accent four parts John Edwards and one part Dan Rather, he has never smoked; even second-hand smoke irritates his sinuses. He did, however, have a few friends who were never quite the same after taking too much LSD.

He believes firmly in the disease model of addiction, and he says that the availability of more pharmaceutical treatments for drug abuse will help shift public opinion: “I want to make this a medical disease with medical options.”

To train the body to attack meth, Owens and his team first spend time designing the right bait. They start with an enormous protein derived from cow blood and attach the protein to many methamphetamine molecules with linker molecules about six carbon atoms long. The end result—a hard-to-miss ‘antigen’ molecule—riles up the immune system and stimulates it to produce antibodies against meth.

Owens sits in his lab holding a small metal model of the methamphetamine molecule, which looks like a hexagon and a half. A zigzagged piece of metal dangling off of the



Molecular matchmaker: Owens (pictured in his lab) designs antibodies to bind methamphetamine.

structure represents the linker molecule. “And the protein,” says Owens, “is the size of this building.” He shakes the methamphetamine model gently. “This becomes guilty by association with the protein.”

When a type of immune cell known as a macrophage encounters the colossal protein-drug combination—the antigen—it engulfs the whole thing. The macrophage then presents fragments of the antigen to other immune cells, a very select few of which subsequently transform into factories for the production of millions of little antibodies against the antigen. Meanwhile, some of the cells that churn out these specific antibodies stick around as memory cells, so that the body can be prepared for later invasions by the same enemy.

If antibodies are formed against methamphetamine (and not for the massive protein it was shackled to), then they will bind tightly to the drug the next time it enters the

body. This binding makes meth too big to cross the blood-brain barrier it formerly whizzed through, and thus prevents it from producing a high.

The really artisanal part of Owens’s work is the fine tuning of the antigen molecules. To make the immune system selectively target meth, everything must fall into place: the choice of protein, the design and placement of the linking molecule and drug, and the luck of the draw amongst the random receptor sites on the surface of immune cells. Creating an effective antigen is, as Owens reminds his lab over and over, a rare event—one that might come along just once in years.

There are two potential paths to pursue once you engineer an antigen that works: you can try to develop it into a vaccine suitable for use in humans, or you can try to use cell cultures to mass-produce the antibodies the antigen elicits.



Beyond the bust: Addiction researchers aim to help put meth “labs” out of business.

These mass-produced antibodies, known as ‘monoconals’, bypass the need to train each individual immune system to churn out its own antibodies. Monoconals react predictably to their targets (in this case, meth) and do so quickly. The effect can be so fast that an infusion of monoclonal antibodies has been shown to stop an overdose in animal testing.

Owens’s lab, which receives a large amount of funding from the US National Institute on Drug Abuse, has a small number of candidate antibodies, some of which they give female nicknames. ‘Nan’ is one of their first best performers—when given to rats taking meth, it decreases the frantic behavior they otherwise show.

To produce large quantities of these antibodies to meth, Owens first exposes rodents to one of his carefully designed antigens and then takes antibody-producing cells from the animals’ spleens. Next, he fuses these cells with other, special cells that never die. The resulting ‘hybridoma’ cells will keep dividing and continuously secreting antibodies. Those that produce antibodies of interest are then cultured in large numbers.

There are challenges to using either vaccines or mass-produced monoconals. When it comes to vaccines, it can take several shots and many months to produce enough antibodies to neutralize foreign particles that enter the blood. Additionally, antibody levels gradually fall off over time.

Monoconal antibodies, meanwhile, are expensive to manufacture and must be infused with intravenous drips in special facilities. Experts expressed doubts about this approach because they thought that a person would have

to receive one antibody per molecule of drug in order to block the high. With some users injecting more than a gram of meth a day, that amount of antibody seemed prohibitively expensive.

However, early results—including those produced by Owens’s monoclonal antibodies against PCP—have suggested that much smaller doses of monoconals can still do the trick⁵. Scientists speculate that antibodies may prefer to dwell in the brain, where they can block the drug’s influence more efficiently.

A one-two punch

In an ideal world, monoclonal antibodies could assist addicts in quitting right away, and vaccines would then provide help over the long run. But faced with a choice, Owens takes the monoclonal approach. “Any time you are going to give a refined medicine that you have complete control of, that’s better,” he says.

Some critics, however, say that drug users on either treatment will just use more drugs to flood the antibodies, ultimately giving their brains a strong enough dose, though this behavior has not yet been seen. “So far we are not seeing that in the animal studies,” says Paul Pentel, who runs experiments with NicVax at the University of Minnesota. He adds that researchers have found “no evidence” of this type of drug-dosage compensation in human clinical trials of the nicotine vaccine.

Experts also suggest that blocking one type of drug high won’t stop users from finding new addictions. “If you block cocaine, they [will] go get cigarettes or Ritalin or amphetamine,” says Roh-Yu Shen, who works on brain changes wrought by addiction at the University of Buffalo in New York.

Owens and other researchers are quick to point out that their products will be just one part of a treatment, along with behavioral therapy and perhaps, someday, drugs to dull cravings. The treatments also won’t do anything for withdrawal symptoms. “Our antibodies are going to be more like the insulin for diabetes,” says Owens. “What doctor would tell a diabetic that they were cured because they were on insulin?” Diabetes requires injections and tough behavior changes. And still, there is no cure, only management.

“People expect a cure, and that is an unrealistic expectation,” Owens adds. “I think the expectation should be years of living drug-free.” The cancer community, he notes, facing a disease without a real cure, has decided that five years cancer-free means the patient has recovered.

Once monoconals and vaccines are on the market, society will have to work out who should receive them and under what circumstances. Ethical questions still remain concerning the possible use of these medications, including their potential use in children and convicted criminals.

Owens and a few colleagues have started a company, InterVax Therapeutics, which will buy their discoveries back from the University of Arkansas and try to market them to drug companies. Their success will rely on a market of addicts with some kind of private or public health coverage.

Back in Lonoke, Lieutenant Kulesa ponders whether a meth vaccine could eventually heal the men and women he spends his days pursuing. “I am all for anything that would help the problem,” he says. But he seems skeptical. “I think there’s a more personal aspect to this. I had one guy who was more addicted to the cook than the drug. It is exciting to them; they are more addicted to trying to make more: better yield, better quality.”

In at least one way, then, Owens and his colleagues are like methamphetamine cooks. Seated around a conference table, sipping on Pepsis and eating lunch, his team talks nonstop about how they might produce large quantities of powerful antibodies. The difference, of course, is that the scientists’ obsession might save lives rather than ruin them.

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