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Opioid Vaccines as a Tool to Stem Overdose Deaths

Researchers are turning to the immune system for help in treating addictior and preventing overdose.

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In October 2020, researchers at Columbia University began enrolling volunteers who were physically dependent on opioid drugs for a new clinical trial—the world's first to test a vaccine targeting these addictive substances. Volunteers who pass a battery of assessments are injected with an analog of oxycodone and immune-stimulati ingredients to urge their bodies to produce antibodies that will bind the opioid—and possibly simil drugs such as hydrocodone—and block them from entering the brain. The hope is that this vaccine would not only prevent the euphoric high that oxycodone users seek, but also protect against overd by averting the disruption of neural circuits that control basic functions such as breathing, explains neurobiologist Sandra Comer, director of the Opioid Laboratory in the Division on Substance Use Disorders at Columbia's Irving Medical Center, and principal investigator of the study.

"It's always a little unnerving to be the first to give a new medication to someone," she says. But she adds that she and her colleagues are "extremely excited" about the recent trial launch because of the potential clinical benefit to people with opioid use disorder (OUD). "I think [this vaccine] has a lot promise as either a stand-alone treatment or as a medication that could be used in combination wit the existing medications [for OUD]."

Opioid overdose is now the leading cause of accidental death in the United States, with record-breaking rates that continue to climb each year. There are currently three US Food and Drug Administration–approved drugs to treat OUDs. (See illustration on page 15.) While these medicatic consistently demonstrate high efficacy in reducing opioid use and the risk of overdose death, the treatments are underutilized for a range of reasons including lack of physician awareness about OU treatment options, stigma against people with substance abuse disorders, and low adherence amon patients due to the frequent dosing required. More than half of people taking these medications

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relapse to illicit opioid use within about six mor after treatment initiation. Researchers who spo with *The Scientist* say that, based on the results animal studies, they anticipate that new opioid vaccines could serve as novel treatments for OU that would provide longer-acting protection against overdose after relapse.

In addition to Comer's first-in-human oxycodor vaccine study, a handful of other immune-based treatments for addiction and overdose are advancing toward clinical trials. Vaccines again heroin and fentanyl are currently in the preclini pipeline, as are monoclonal antibodies targetin these drugs. Despite various attempts in the pas three decades to bring such therapies to market including a few nicotine and cocaine vaccines th helped some people in clinical trials, developme in these areas has waned. With opioid-related deaths increasing at alarming rates, however, researchers say they are hoping that renewed efforts to vaccinate against addiction will finally prove successful.

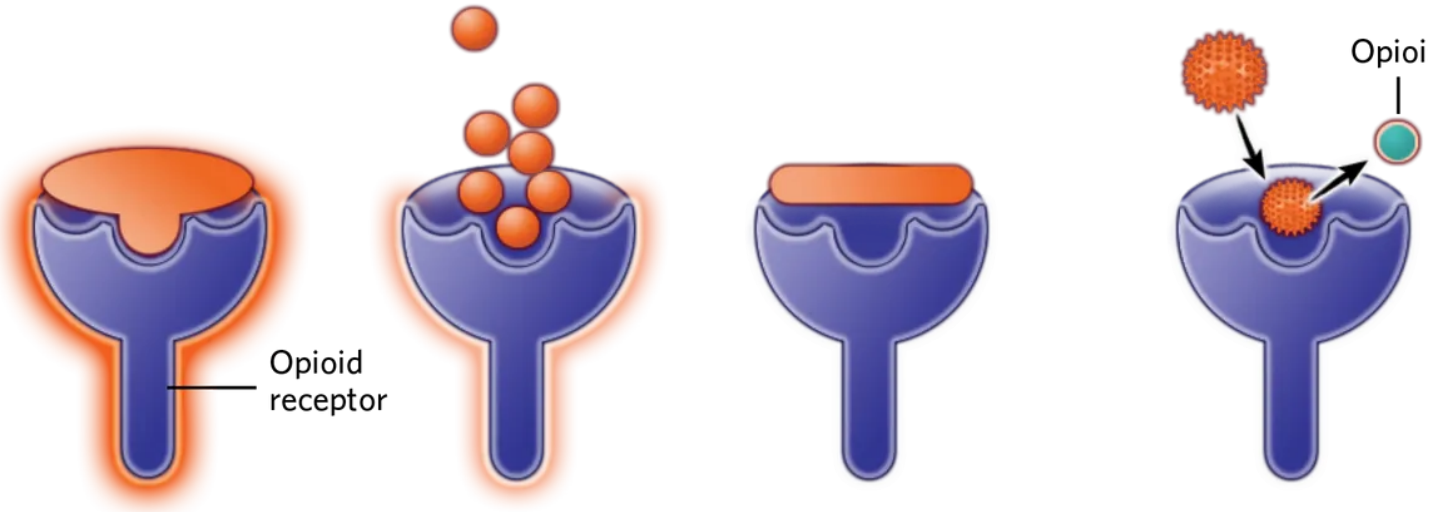
Opioid overdose is now the leading cause of accidental death in the United States.

Clinician Paul Christo, an associate professor of anesthesiology and critical care medicine at Johns Hopkins Medicine in Baltimore, says he's enthusiastic about the prospect of having a novel strategy protect his patients. He adds he has a special interest in the opioid crisis and has noticed the uptick patient deaths from opioids, both alone and in combination with other drugs. In the 12-month peri ending April 2021, more than 100,000 people died from drug overdoses in the country—nearly 30 percent more than the number reported for the same period the previous year. Roughly 75 percent these deaths were attributed to prescribed and illicit opioids, primarily the synthetic opioid fentany and its analogs.

“I think [vaccination is] an exciting concept because we certainly need other means—well, first of a we need additional means to control pain, and we also need other means to stave off overdose risk,” says Christo. “If we could immunize patients against the risk of overdose, that would be amazing.”

APPROVED DRUGS FOR OPIOID USE DISORDER

While it may seem counterintuitive, some drugs used to treat opioid use disorder (OUD) activate opioid receptors in the brain. Methadone is a full opioid agonist, binding to and activating opioid receptors while blocking the binding of other opioids. It is longer-acting than opioids such as herc and oxycodone, however, so it can provide a mild, controlled "hit" to reduce withdrawal symptoms such as drug craving, gastrointestinal distress, and accelerated heart rate. Another OUD treatmen approved in the US is buprenorphine, a partial opioid agonist that binds to but only partially activates the receptor. A third option, naltrexone, is an opioid antagonist, meaning that it blocks opioids from binding the receptors without any activation. In addition, the overdose antidote naloxone can be used to treat overdose itself. It is an opioid antagonist that knocks opioid molecul off the opioid receptors and takes their place.



Drugs for OUD			Drug for reversing overdose
Methadone	**Buprenorphine**	**Naltrexone**	**Naloxone**
Binds and fully activates	Binds and partially activates	Binds but doesn't activate	Knocks opioid off receptors

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Cocaine and nicotine vaccines falter in trials

While the first studies demonstrating the ability of a vaccine to produce anti-opioid antibodies in animals were conducted in the 1970s, concerted efforts to develop an opioid vaccine didn't get underway until much later, inspired by attempts to immunize people against other common drugs abuse: cocaine and nicotine.

As small molecules, addictive drugs typically evade detection by the immune system. To elicit an immune response against these substances, researchers fuse a synthesized analog of the drug to an immune-triggering protein and pair it with adjuvants to further stimulate the production of antibo that would bind to the drug molecules and sequester them in the blood. "The antibodies are like a sponge that go around soaking the drug up," explained chemist and immunologist Kim Janda, direc of the Worm Institute for Research and Medicine at Scripps Research. This prevents the drug molecules from crossing the blood-brain barrier and binding to opioid receptors. Instead, they are converted into inactive metabolites and excreted.

Starting in the 1990s, several groups explored cocaine and, later, nicotine vaccines, with some candidates advancing to Phase 2 or 3 clinical trials funded by the National Institute on Drug Abuse (NIDA). They ultimately proved only moderately effective, however, helping only a subset of participants. In multiple trials investigating nicotine or cocaine vaccines, only about a third of participants—those with the highest antibody levels—demonstrated longer abstinence than people receiving placebos. "Patients produced inadequate titers of antibodies and there was significant variability in the levels of antibodies achieved after vaccination between clinical trial participants," explains Nora Volkow, director of NIDA. Although these clinical programs were terminated, researchers at Weill Cornell Medicine are currently investigating a cocaine vaccine candidate in a NIDA-funded Phase 1 clinical trial, while others continue to investigate the approach in animal models.

Janda has been involved in anti-addiction vaccine development throughout this time, and in fact, h group has been credited with creating the first feasible cocaine vaccine. But after reports in 2009 linked an increase in HIV cases in developing countries to shared needles for heroin use, Janda pivoted to the idea of opioid vaccines. He recalls thinking, "Well, maybe we could help curb . . . the increase in HIV by trying to develop a vaccine against heroin."

The heroin vaccine, which Janda has patented, took about a year to make, he says, and soon demonstrated its utility in rats, leading to rapid generation of antibodies and blocking the pain-inhibiting effects of the drug as well as decreasing the chances that the animals would begin self-administering the drug when it was made available to them. Janda's team subsequently developed vaccines against numerous other opioids, including oxycodone, hydrocodone, and fentanyl, and thc treatments have shown similar promise in preclinical research. In the past five years, their heroin a fentanyl vaccines became the first of their kind and the first to succeed in nonhuman primates. Antibodies generated by the heroin vaccine led to a greater than fourfold reduction in heroin poten in rhesus monkeys, and the fentanyl vaccine resulted in a tenfold drop in drug potency and a sixfol increase in fentanyl plasma levels, supporting the idea that the drug is being sequestered in the blo With the fentanyl vaccine, Janda was "interested to see if a vaccine could be developed to block something that's much more potent" than the previously tested opioids. "I was interested just to see we could push the limits." In 2020, his team tested a dual fentanyl/heroin vaccine in rats and obser a 7.5-fold decrease in the potency of a fentanyl/heroin mixture after three shots of the dual vaccine.

"Kim Janda [is], I would say, the grandfather of this field," says immunologist and pharmacologist Marco Pravetoni, a professor of psychiatry at the University of Washington in Seattle and an invent of the oxycodone vaccine being tested in clinical trials at Columbia University. "He's done tremendo work in this area."

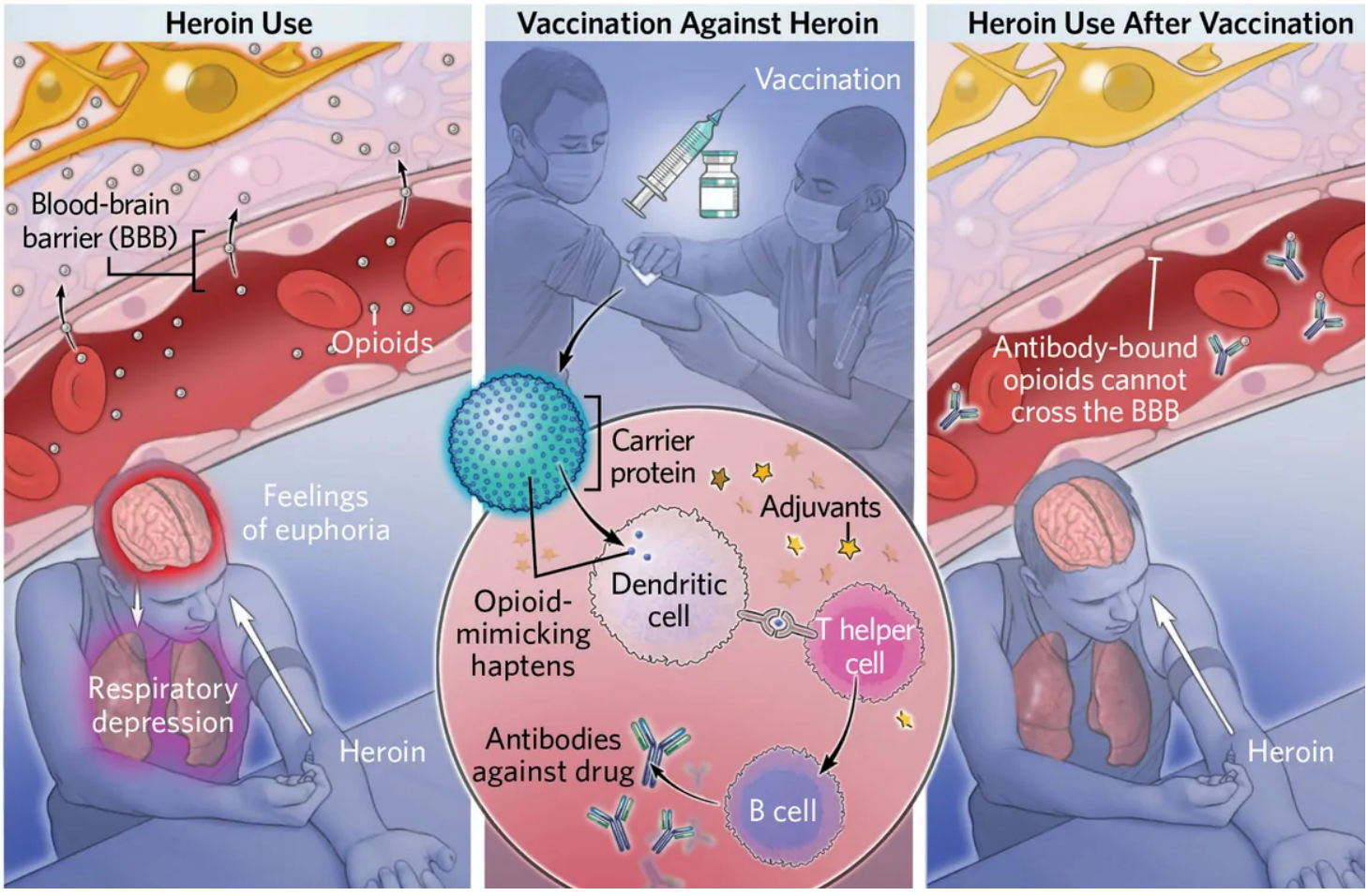
Cessation Therapeutics, a California-based company founded in 2017 where Janda serves as scienti advisor and board member, is continuing to develop the combination heroin and fentanyl vaccine created by Janda's group, says Cessation research and development director Paul Bremer, who is on Janda's former graduate students. But for now, the company is prioritizing an anti-fentanyl monoclonal antibody (mAb), an approach also being pursued by a handful of other groups, includi Pravetoni's. These antibodies are generated in the lab by giving animals an anti-fentanyl vaccine, ar researchers involved in their development say the treatment has the potential not only to treat OUI and protect against overdose, but to reverse an overdose in progress. (See "Monoclonal Antibodies a Shortcut to Vaccination" on page 18.") Bremer says the company is aiming to move its monoclonal antibody into Phase 1 clinical trials in the near future with NIDA funds as part of the National Institutes of Health's Helping to End Addiction Long-term (HEAL) Initiative.

"We'll be submitting the IND later this year, and soon after that, we'll be clear to start our Phase I clinical trials," Bremer forecasts, adding that while the opioid vaccines "are further behind . . . we

believe getting the IND on the mAb will help pave the way for us to move the vaccines toward the clinic more quickly."

VACCINE-INDUCED BLOCK

Due to their small molecular size, opioids can cross the blood-brain barrier (BBB) to cause both th euphoria that makes such drugs so addictive and the adverse effects including the respiratory depression that can cause fatal overdose via inhibition of neural networks that regulate breathing (left panel). To fight opioid use disorder (OUD) and reduce overdose deaths, scientists have designed a handful of experimental vaccines, which are just beginning to enter human testing. These experimental vaccines involve a carrier protein studded with analogs of the opioid, called haptens, combined with adjuvants that strengthen the overall immune response (middle panel). Antibodies generated against haptens will bind to the opioid, blocking it from crossing the BBB d to the antibodies' large size (right panel). The hope is that if people recovering from OUD receive vaccine targeting their drug of abuse and then relapse, they will not experience respiratory depression that can lead to overdose or the euphoric effects that reinforce the drug-seeking behavior.



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Testing opioid vaccines in humans

For Carl Alving, emeritus senior scientist in the Laboratory of Adjuvant and Antigen Research at th Walter Reed Army Institute of Research (WRAIR), the concept of immunizing people against substance abuse and overdose wasn't on his radar until he had NIDA's Volkow over for a dinner par in 2010. She told Alving that the agency had been sponsoring research on vaccines against drugs of abuse and mentioned the nicotine and cocaine vaccines that had failed in clinical trials despite showing promise in preclinical studies. She says that she believed researchers needed stronger vacc adjuvants to elicit a more robust immune response.

"That's where I came in," says Alving, who is now retired and notes that he is speaking for himself a not on behalf of the US government. "At Walter Reed, we specialize in making strong and safe adjuvants" along with other vaccine components. He was working as a researcher with the US Milit HIV Research Program (MHRP) in the division of retrovirology at WRAIR, attempting to develop vaccine against HIV, when Volkow encouraged him to apply for NIDA grants to fund research on heroin vaccines. "NIDA became more interested in opioid vaccines because there was, and still is, a need to expand the available treatment options for opioid use disorder," says Volkow. "There was als need to stem the transmission of HIV among people who inject drugs during this time, and treatin opioid use disorder is an important strategy for reducing risk behaviors associated with acquiring a transmitting HIV." Volkow's and Alving's labs struck up a collaboration, initially aiming to create a dual vaccine that would prevent HIV infection while treating heroin dependence and reducing the of overdose, but ultimately moving forward with a more narrowly focused heroin vaccine, which performed well in mice and rats in the mid-2010s. The Army and the Department of Health and Human Services, which houses NIH, patented the technology; Alving is named as an inventor.

If current manufacturing and testing efforts are successful, that heroin vaccine will proceed to hum testing with support from a NIDA grant, according to Gary Matyas, chief of the Adjuvants and Formulations section at WRAIR who worked with Alving on the vaccine and who is also named as inventor on the patent. "Although overdose deaths due to heroin have plateaued over the last year, heroin overdose deaths remain a problem, so there may still be a therapeutic role for the heroin vaccine," he says. Matyas and NIDA colleagues have since developed candidate fentanyl vaccines, fo

which they have a patent pending, as well as a combination fentanyl-heroin vaccine. Most recently, they developed monoclonal antibodies to fentanyl and its analogs, for which they have applied for a provisional patent, Matyas says.

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>
> **—Paul Christo, Johns Hopkins Medicine**

As the collaboration between WRAIR and NIDA got underway, Pravetoni, then at the University of Minnesota, and colleagues were in the early stages of their work on a vaccine for oxycodone, a main driver of opioid overdoses at the time. In response to shifting trends in overdose deaths over the past decade, the team is now developing a heroin vaccine and has received funding from NIDA to create vaccines and monoclonal antibodies against fentanyl and fentanyl analogs, the synthetic opioids largely driving the ongoing surge in overdose deaths. They hope to progress to clinical testing with one of these fentanyl candidates next year.

Meanwhile, in the current Phase 1a/1b trial of their oxycodone vaccine candidate funded by the HEAL Initiative, the investigators will enroll up to 24 volunteers. They aim to evaluate the vaccine's safety, degree of antibody production, and preliminary efficacy before proceeding to Phase 2 to demonstrate efficacy in a greater number of patients. "The way it works is that the patient would receive a series of injections of the vaccine," explains Comer. Specifically, there are three shots given over six weeks and then a fourth shot three months later. During weeks-long inpatient stays in the hospital before and after vaccination, investigators will give the participants various doses of oxycodone and ask questions such as, "Do you feel high?" and "Do you like the dose?" If the vaccine is working as intended and generating adequate antibody levels, Comer says, they expect to see reductions in ratings of "drug liking" after vaccination. The researchers will follow the same process with lactose powder as the placebo, or negative control, and with heroin as a positive control. Comer says they anticipate no change in participants' ratings of heroin following vaccination, because the antibodies should not bind to the drug.

Pravetoni, now at the University of Washington, will test participants' blood samples back at a still-active University of Minnesota lab to assess their immune responses to the vaccine. In addition to tracking antibody responses, Pravetoni's team will be measuring B cell activity before and after vaccination to see how it correlates with participants' antibody production against oxycodone. Among vaccinated mice, he and his colleagues previously observed a stronger immune response against

oxycodone in those with greater B cell activity prior to vaccination. If they find a similar pattern in t clinical trial, Pravetoni says, this could ultimately serve as a biomarker to identify patients who are most likely to benefit from a vaccine.

Comer notes that while the antibodies generated would not be able to bind a different chemical structure like heroin, they should be able to bind not just oxycodone but also chemically similar dru "Oxycodone, hydrocodone, oxymorphone should all be recognized by the antibody." For that reason the vaccines shouldn't interfere with the actions of other opioids such as morphine when needed fo pain control, she says, nor should they influence a patient's response to OUD medications or naloxc the treatment that rapidly reverses opioid overdose, which all act on the opioid receptors in the bra

A risk that should be considered, says Christo, is that individuals vaccinated against one opioid may simply use another opioid if they relapse. In deciding which types of participants to enroll in the oxycodone trial, Comer and colleagues considered this scenario and opted to recruit volunteers who primarily use heroin or fentanyl. They were concerned that those with OUD who use oxycodone as prescription medicine for pain management may turn to something more potent, like fentanyl, if th vaccine turns out to be effective in blocking oxycodone.

"The plan is to ultimately have a multivalent vaccine that targets multiple opioids—oxycodone, hero fentanyl. So in a clinical setting, someone using oxycodone would receive all three vaccines in order protect against 'opioid switching,'" Comer explains. "The FDA did not allow us to test a multivalent vaccine at this stage of development, however, until we first gather safety information about each individual vaccine."

Future directions for opioid vaccines

David Streem, chief of psychiatry at Cleveland Clinic Lutheran Hospital and medical director of the facility's Alcohol and Drug Recovery Center, says he is growing disillusioned with treatment approaches that require daily adherence like some of the medications currently used to treat OUD. Those daily regimens, he notes, are difficult to sustain for many patients. Two of these treatments, naltrexone and buprenorphine, can be administered monthly by injection, and Streem recalls a pat who asked if she could switch to that option, even though it would require more frequent visits to Streem for injections, because she only wanted "to have to make one good decision a month." He sa that a vaccine, which he envisions being used in combination with OUD medications as well as oth treatment measures such as therapy and recovery groups, would similarly present "opportunities to provide treatment that doesn't rely on a daily commitment to compliance."

Although Christo recognizes the potential value of an opioid vaccine, he does have some practical concerns, including the need for an alert mechanism to inform medical providers of the vaccinatior status in case opioid medications are needed for pain control in a medical emergency and the patie unconscious. If the provider sees a note in the patient's electronic health record indicating they hav been vaccinated against oxycodone, for example, the clinician can use morphine or other opioids to manage the patient's pain. Christo also wonders who will pay for the vaccines and whether insuran companies will cover their cost.

Before these therapies even reach the clinic, however, funding for additional trials may present an ongoing challenge in moving opioid vaccines forward. Pravetoni says he believes that because of the stigma against people who use drugs and the perception that they are a difficult population to treat some companies might hesitate to invest in such addiction interventions. Janda agrees. "The main barrier is that many people see addiction as a moral failing on the part of the individual," he says.

For him, the continued passion for this work comes from the people affected by addiction who have reached out to him over the years. "I've met so many families whose lives were torn apart by addicti he says. "We can't put our heads in the sand; we have to try to find solutions." Volkow echoes that sentiment. "Novel approaches like an opioid vaccine, if proven to be safe and effective, could help sa some of the many lives lost to opioids."

Monoclonal Antibodies as a Shortcut to Vaccination

In parallel to pursuing opioid vaccines, which aim to trigger the immune system to generate antibodies against the addictive drugs and protect against overdose, some researchers are looking make the antibodies themselves, by immunizing rodents or other animals with just such a vaccine Researchers can then isolate the resulting opioid-specific B cells and fuse them with immortal myeloma cells to form long-lived antibody-generating cells. From these, they can harvest antibodi that animal studies suggest could protect human recipients against future drug use and overdose, and more critically, help treat acute overdose.

While the vaccines produce a large number of polyclonal antibodies with variable binding affinity for the target drug, the use of monoclonal antibodies involves "selecting one that you think is going to be the best, and you can make a lot of it," explains Scripps Research chemist and

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it," explains Scripps Research chemist and immunologist Kim Janda. This process results in antibodies that are likely to bind most tightly to the drug molecule and keep it from reaching the brain—or, as animal studies with methamphetamine and PCP show, even pull it out of the brain, if the antibody has a higher affinity for the drug than its receptors. This property could make a monoclonal antibody (mAb) an effective treatment even in the midst of an opioid overdose. Indeed, in a 2019 mouse study, Janda and his team found that their mAb candidate reversed the effects of fentanyl and its analog carfentanil when administered 30 minutes after the opioid dose (*J Am Chem Soc*, 141:10489–503, 2019).

Another advantage of monoclonal antibodies over vaccines is that there is no need to wait for the immune system to produce antibodies itself, a process that can take weeks or months in animal models. "As soon as you infuse it, it's on board working," Janda says of a monoclonal antibody treatment. He adds that using monoclonal antibodies would allow clinicians to control the dose administered based on the degree of intoxication and other factors.

On the downside, however, the 2019 rodent work indicates that protection from monoclonal antibodies is more short-lived than that from vaccines—on the order of several weeks, compared t a few months or more when vaccinated. Experts propose that when it comes to treating OUD, monoclonal antibodies might be used in conjunction with vaccines to help bridge the gap while immunity from the vaccine is building. And in terms of treating acute overdose, monoclonal antibodies boast a longer half-life than naloxone, the only existing treatment to reverse overdose, and might thereby reduce the risk that opioids remaining in the blood would cross the blood-brai barrier and bind to the opioid receptors following naloxone metabolism. Indeed, the rodent study suggests that the two strategies could be combined for optimal effect. Janda anticipates that it ma be easier to gain US Food and Drug Administration approval for monoclonal antibodies as a treatment for overdose and then use them off-label as a treatment for OUD.

An anti-fentanyl antibody and a combination heroin and fentanyl vaccine developed by Janda's group are slated for further development and clinical testing by Cessation Therapeutics, which employs two of Janda's former graduate students and where he now serves as scientific advisor an board member. Meanwhile, teams led by University of Washington psychiatry professor Marco Pravetoni and by Gary Matyas at the Walter Reed Army Institute of Research are independently

developing mAbs against fentanyl and fentanyl analogs as well; the two researchers say they hope advance the therapies to clinical trials in the near future.

In addition to their potential value in preventing and reversing accidental overdose in people who use drugs, Janda and neurobiologist Sandra Comer, principal investigator of the clinical trial currently testing an oxycodone vaccine at Columbia University, note that monoclonal antibodies could also be used in national defense to prevent casualties related to the use of chemical weapons such as the aerosol deployed by the Russian military in 2002 to incapacitate Chechen rebels holding hostages in the Dubrovka Theater in Moscow. The aerosol contained the fentanyl derivative carfentanil and killed around 130 hostages and 40 rebels.

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