Dynamic detox

By Tracey Baas, Senior Editor

A team at **The Scripps Research Institute** has created a heroin vaccine that, unlike conventional single-antigen vaccines, displays multiple drug-like antigens. The vaccine led to robust antibody titers that blocked the effects of heroin in rats, and the team now plans to evaluate the extent of vaccine protection by giving animals escalating doses of heroin.[1] As opposed to current options for preventing heroin addiction, the new vaccine does not carry a risk of abuse or diversion and should not raise compliance issues.

Typically vaccines lead to production of antibodies that target one antigen. Although the Scripps vaccine initially induces the production of antibodies targeting heroin, the vaccine is slowly broken down by the body, allowing the production of antibodies targeting heroin's metabolites 6-acetylmorphine and morphine. Heroin, 6-acetylmorphine and morphine all contribute to the psychotropic effects of the drug (*see* **Figure 1, "Immunochemically dynamic vaccine"**).

Since the 1970s, heroin addiction has been treated primarily with methadone. Methadone itself is an opiate but has a considerably weaker psychotropic effect than heroin. Methadone treatment avoids heroin withdrawal symptoms, but long-term use can lead to side effects such as constipation, weight gain, decreased libido and menstrual irregularities.

The other option for treating heroin addiction and preventing relapse is opioid antagonists, which inhibit the effects of heroin but can also block the effects of endogenous opioid peptides and lead to negative emotional effects. Also, opioid antagonists do not alleviate withdrawal symptoms.

For both options, side effects contribute to low patient compliance and heroin relapse. Thus, a Scripps team reasoned that a vaccine capable of specifically blocking heroin's effects would be an attractive alternative.

However, the heroin molecule itself is too small to elicit an immune response. Thus, the researchers synthesized and attached the molecule to a carrier protein to provide a sufficiently large antigenic entity to present to the immune system.

To further increase the immune response, the team adsorbed the immunoconjugate to alum, providing both an adjuvant and a surface that allowed the body to slowly metabolize the heroin-like immunoconjugate.

Team leader Kim Janda, a professor in the Department of Chemistry at Scripps, hypothesized that because the alum surface provides a protected environment, hydrolysis of the heroin immunoconjugate would be slowed and would allow three different forms of the vaccine to be present: the heroin-like, the 6-acetylmorphine-like and the morphine-like form.

The rate of metabolism is important because heroin and 6-acetylmorphine are lipophilic molecules that cross the blood brain barrier more rapidly than the less lipophilic morphine, said Janda. Once psychoactive molecules make it into the brain, antibodies are unable to reach them.

The team used ELISAs to show that vaccinated rats had antibodies

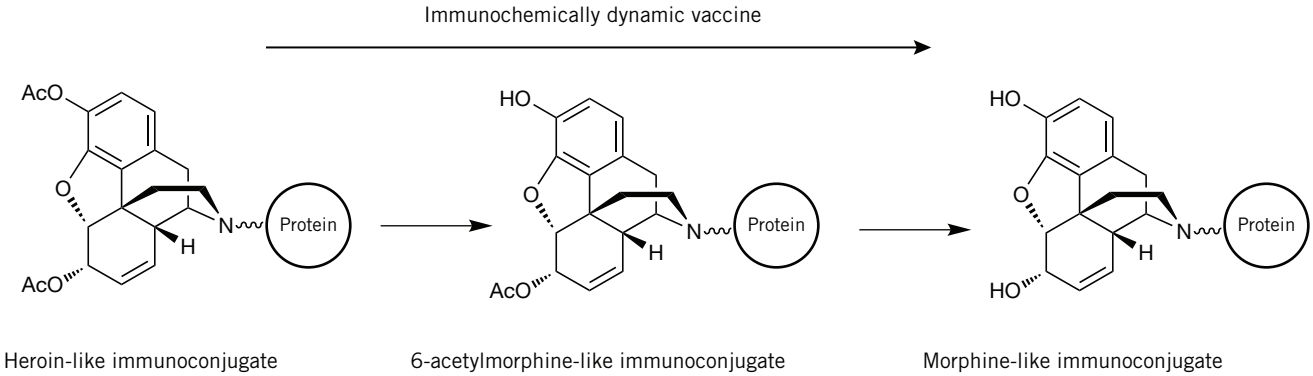

Figure 1. Immunochemically dynamic vaccine. The heroin molecule itself is too small to elicit an immune response. Thus, a team from **The Scripps Research Institute** attached the molecule to a carrier protein to provide a sufficiently large antigenic entity to present to the immune system. Typically vaccines lead to production of antibodies that target one antigen. Initially, the Scripps vaccine works the same way, with the heroin-like vaccine leading to production of antiheroin antibodies. However, the body slowly metabolizes the vaccine, resulting in 6-acetylmorphine-like and morphine-like vaccines. This leads to production of antibodies targeting those two psychotropic metabolites, demonstrating the vaccine's dynamic aspect. (Figure based on Figure 1 in ref. 1.)

that bound heroin and heroin's psychotropic metabolites but did not bind endorphins, the opioid agonist methadone or the opioid antagonists naltrexone and naloxone. This suggests the vaccine would not affect the body's endogenous endorphins and could be used in conjunction with heroin rehabilitation therapies.

About 60% of vaccinated rats stopped heroin self-administration compared with 0% of carrier protein–vaccinated rats.

In thermal and mechanical sensitivity tests, vaccinated rats that received a dose of heroin showed responses that were similar to their original heroin-free baseline responses. Also, the vaccine did not block the effects of the opioid analgesic oxycodone, suggesting that options for pain relief are still possible.

"For traditional infectious diseases if we find the correct target, a vaccine should be effective. However, for drugs of addiction, we not only deal with the correct target to stop the addiction but also the challenge of human behavioral and habitual aspects, for which a vaccine is not effective."

—Raafat Fahim, Nabi Biopharmaceuticals

Those data are important because patients receiving heroin antagonists or vaccines could potentially require either high doses of opioid analgesics to treat pain or a different class of pain drugs altogether.

Data were published in the *Journal of Medicinal Chemistry*.

"The work suggests that it is evidently feasible to develop antidrug vaccines—the challenge for those developing such vaccines is to achieve valuable clinical benefits without unleashing intolerable complications, such as the nightmare scenario of highly successful blockade which then needs reversal for essential pain relief of a road traffic accident, broken leg or even toothache," said John Strang, director of the Addictions Department at **King's College London**.

Heavy on metabolites

Nora Volkow, director of **NIH**'s **National Institute on Drug Abuse**, said Janda's strategy "is attempting to overcome the obstacle presented by the fact that heroin's metabolites are also psychoactive, such that the antibodies would need to specifically target a broader spectrum of related molecules."

She said the next steps would be to test the vaccine's safety in humans, optimize its dose curve and establish whether the vaccine provides the expected protection.

Raafat Fahim, president and CEO of **Nabi Biopharmaceuticals**, agreed it was "an intelligent approach to vaccine design" but thinks the La Jolla researchers will "face similar challenges as other vaccines of addiction in moving the vaccine from animals to man. Many times a vaccine that looks great in an animal model shows just fair results when tested in man," especially for addiction vaccines.

"For traditional infectious diseases, if we find the correct target, a vaccine should be effective," he said. "However, for drugs of addiction, we not only deal with the correct target to stop the addiction but also the challenge of human behavioral and habitual aspects, for which a vaccine is not effective."

"Monitoring safety and optimizing the vaccination schedule to elicit high antibody production can be done in nonaddict volunteers, so those studies are more straightforward," he continued. "Human protection studies are more challenging because addicted patients need to be enrolled and the studies have to be conducted in a safeguarded clinical setting."

John Marsden, a member of the Addictions Department at King's College London, said protection studies will need to have stringent safety monitoring. "It may be possible to overcome the effect by injecting a very large dose of heroin. Establishing efficacy may also be a real problem because unfortunately there could be a very large placebo effect which will suppress the effect size."

Janda's team is evaluating the efficacy of the vaccine in relapse and self-administration mouse models involving escalating doses of heroin. He said the vaccine might do the most good in developing countries where i.v. drug use is prevalent and methadone treatment is not an option.

The researchers are collaborating with a group at the **Walter Reed Army Institute of Research** to see if it is feasible to develop a dual-purpose vaccine that protects against HIV and treats heroin addiction in a single shot.

The work described in the paper is unpatented and available for licensing from The Scripps Research Institute Office of Technology Development. Janda is interested in finding a partner for preclinical evaluation of the vaccine and for an IND submission.

There are no FDA-approved vaccines for any type of drug addiction. Indeed, Nabi's NicVax nicotine addiction vaccine failed in a Phase III trial this month.

The next most advanced addiction vaccine is **Celtic Pharmaceutical Holdings L.P.**'s cocaine–recombinant cholera toxin B immunoconjugate (TA-CA), which is in Phase IIb testing for cocaine addiction.

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