

FINANCING SCIENCE



BRIDGING
the
VALLEY
of
DEATH

Cocaine Vaccine
Efforts a New
Financing Model for
Drug Development

By Mark Meier



The “war on drugs,” that well-worn phrase trotted out by presidents past and present,

is today almost devoid of real strategic meaning, especially when it comes to the cocaine epidemic that has swept our nation. Supply-side theorists advocate destroying coca fields and tightening America’s borders. Demand-side advocates insist on more Drug Abuse Resistance Education in schools and stiff sentences for cocaine—the better to lower demand on the streets. Neither seems to be working very well.

Now, an experimental vaccine to treat cocaine addiction may well upend the stale strategies that underpin the “war on drugs.” If the vaccine proves effective in clinical trials, then “Just Say No” may take on an entirely new meaning: your body will agree even if your mind wants to say yes.

If the vaccine does prove to be efficacious, it is not just the science that should be applauded. So, too, should the public- and private-sector financing model that would have funded the vaccine all the way to the marketplace—something that hardly ever happens with vaccines in the world of drug development. The applause, however, for bridging this financial “valley of death” might just stop there. The reason: profitability is not at all assured even if the last clinical trials prove successful.

Public health officials must then answer the question of “who gets vaccinated,” which in turn will determine just how much money the private investors behind the cocaine vaccine will reap in profits from the more than decade-long effort to bring it to market. This cocaine vaccine, then, boasts a number of potential lessons for scientific researchers, public and private investors in vaccine development, and public health professionals and policymakers.

A NOVEL VACCINE PATHWAY

Researchers at the Baylor College of Medicine in Houston requested permission in December 2007 from the Food and Drug Administration to begin Phase III clinical trials for a vaccine called TA-CD. These late-stage clinical trials will test the efficacy of TA-CD’s ability to blunt or even to prevent cocaine’s effects on users among a group of several hundred humans, which if successful would move the drug very close to commercialization.

Reaching Phase III trials is a monumental achievement, as very few drugs make it that far in the research-and-development and regulatory approval phases of development. And for TA-CD, it’s been a long time coming. The TA-CD vaccine first made headlines in 1996,

when Barbara Fox and collaborators published in *Nature Medicine* that rats could be inoculated against cocaine's euphoria.¹ The same approach then proved feasible in early stage clinical trials with about 20 humans. By attaching the cocaine molecule to an inactive cholera protein, the TA-CD vaccine stimulates the subject's immune system to produce antibodies that bind to cocaine and prevent it from passing from the blood into the brain, which means vaccinated users no longer experience the same high from cocaine, and hence, demand it less.

The initial vaccination is usually administered in several shots over weeks or months, which trains the body to associate cocaine with cholera. Results from 2005 suggest a booster shot is necessary every four months to maintain the vaccine's efficacy, which has been enough time for some people in trials to cut their cocaine use significantly.²

TA-CD is not the first vaccine to combat drugs. In 1974, for example, Dr. Charles Schuster (then at the University of Chicago) developed a vaccine that prevented monkeys from getting high on heroin, but he and other researchers opted not to pursue its application to humans because users could easily switch to other opiates. One of those other opiates, methadone, is commonly used to wean heroin addicts from their habit. It is not yet clear if TA-CD will suffer the same drawbacks, or if users could increase their dosage dramatically—and dangerously—to defeat the vaccination. The initial trials, however, have found no users tried either approach to circumvent TA-CD.

The idea of fighting addictions—including cocaine—with vaccines, however, did not end with methadone. The National Institute of Health's National Institute on Drug Abuse has emphasized that approach since it founded the Medication Development Program in 1990. The federal government today currently lists around 200 NIDA-funded clinical trials that use drugs to change how cocaine and your brain interact.³

Most of those drugs approved for actual use in the marketplace were first approved for other uses but also showed some ability to dampen cocaine's

impact by affecting brain function. Modafinil, for example, is sold as Provigil to treat narcolepsy. Disulfiram (better known as Antabuse) makes people crave cocaine less and feel much more paranoid when they take it, similar to how Antabuse makes people ill when they imbibe alcohol. A third drug, baclofen, started as a muscle relaxant.

Yet another drug, buprenorphine—which can be injected during surgery as a painkiller—also counters cocaine when taken orally, though it has been studied more as a tool to fight heroin addiction. Buprenorphine will soon enter a large trial on prison inmates to see if it reduces how much they use heroin and, secondarily, cocaine, after they return to regular life in Baltimore.

Among all these drugs, however, only the TA-CD vaccine stops cocaine from interacting with the brain at all. It arrests the narcotic in the bloodstream, where it can be metabolized into less harmful pieces. That is its physiological revolution.

A NOVEL FINANCIAL PATHWAY

The financial revolution is that a vaccine that does not target an especially wealthy or wide audience may still make money for its private investors. TA-CD development built a novel bridge over the so called “valley of death” funding gap between basic biomedical research and development and—perhaps—eventual drug commercialization.

Public money supported the initial research on demand-side efforts to counter cocaine addiction, as is almost always the case in experimental efforts to develop drugs for markets limited in size or lucre. But public money then also helped finance the development of the vaccine at later stages of its development alongside private, venture capital investors as the drug passed one test after another.

The leading researcher on the TA-CD vaccine trials, Thomas Kosten, today has \$3 million in grants from NIDA to study cocaine treatments, and has spent about five times that much in previous grants since the late 1990s. Kosten ran his earlier trials at

a Veteran's Administration hospital in New Haven, Connecticut. Now that Kosten has moved from Yale to Baylor, he runs the trials from the Michael DeBakey VA Hospital in Houston.⁴

Celtic Pharma, a Bermuda-based firm that invests in drug development start-up companies around the world, bought Xenova, a British company working on the TA-CD vaccine in August 2005. Kosten received money from Xenova for consulting but has cooperated with many companies as the drug changed hands several times during clinical trials over the previous decade. When Celtic Pharma bought Xenova, the acquired company was concurrently developing a vaccine approach to nicotine with similar success under the name TA-NIC. That drug will likely begin Phase III trials soon, and competitors are working on their own versions.

Previously, in 2001, Xenova had acquired both vaccines from another British company, Cantab Pharmaceuticals. Cantab, in turn, got the drugs when it bought the vaccine program of ImmuLogic Pharmaceutical Corp., operating in Massachusetts with nominal headquarters in Delaware. ImmuLogic also worked on allergy medications and held the patent for the technique common to TA-CD (known as IPC-1010 at the time), and TA-NIC: binding addictive substances to immunogenic compounds, an approach known as hapten-carrier conjugates.

Tens of millions of dollars changed hands in these three deals.⁵ But it all started when NIDA awarded ImmuLogic a Small Business Innovation Research grant of \$700,000 in 1996 to develop a vaccine for humans.⁶ Now, more than a decade later, public and private financing has carried the vaccine to Phase III clinical trials, which are about to commence and are expected to last one to two years.

Celtic Pharma (according to its website)⁷ sees these types of drugs as potential blockbuster investments that could “build real value by driving them through the final stages of the approval process” with the intention to “achieve extraordinary returns for its investors by monetizing these important and

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innovative drugs.” A mix of biotech and hedge fund veterans, Celtic Pharma stands at the end of a long chain of investors, though without NIDA funds driving the research and federal hospitals providing some of the infrastructure through the first phases of clinical trials, the TA-CD vaccine might never have emerged from the Petri dish.

The upshot: federal dollars spent over the entire course of the development process, in tandem with lots of additional private sector funding, led to what may well be a marketable vaccine that could well produce a public good—fewer people in the thrall of cocaine addiction.

THE PUBLIC HEALTH PATHWAY

The story of TA-CD doesn't end there, however, either scientifically or financially. If the clinical trials are as successful as the developers of the vaccine hope they will be, then policymakers in the United States and abroad will have plenty to consider. Indeed, this potential physiological revolution has already prompted much discussion about the public health implications of vaccinating current or possibly future users.

With TA-CD facing only a few—though still significant—hurdles on its way to the marketplace, questions have been arising about this novel way to tame a social problem with the standard tools of pub-

lic health. Cocaine addicts would probably benefit from the vaccine, and hypothetically the U.S. government and public health officials in other countries might be able to contain the spread of cocaine contagion by inoculating parts of the general population.

That hypothetical, however, in turn has already raised questions about who might be required or encouraged to try the vaccine and under what circumstances. Should TA-CD be considered in the standard childhood battery of measles, mumps, and rubella shots? Should it be administered to all adolescents? Or should it be limited to more definable “at risk” groups, such as those arrested for drug use who are about to be released from prison?

Less sanguine comparisons have been made to the contraceptive Norplant,⁸ which U.S. courts in the early 1990s offered women in the criminal justice system as an alternative to tougher prison sentences. Critics said Norplant was a dubious way of biologically-based social control to shrink the so-called underclass. Norplant was later yanked from U.S. markets because the drug displayed some significant side effects.

The National Academy of Sciences is already considering similar questions, having published in 2004

a book on immunotherapies for addiction entitled *New Treatments for Addiction: Behavioral, Ethical, Legal, and Social Questions*. That study essentially recommended thinking long and hard about using immunotherapeutic drugs to treat drugs of abuse, including how to make vaccines more permanent, how to protect people from coerced vaccination, and how to anticipate changes in the drug market or users’ behavior in response to the vaccine.⁹

How public health officials decide to distribute the TA-CD vaccine—providing it clears Phase III clinical trials and is then approved for sale to the general public by the U.S. Food and Drug Administration—will be enormously consequential financially for TA-CD’s investors and society at large. In the end, those decisions may well determine whether this novel approach to researching and financing this public good succeeds for all involved. And if it works well for all, then it may well spark other private-public partnerships in search of other novel techno-chemical methods to tackle the scourge of addictive drugs in our society today. sp

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NOTES

- 1 Barbara Fox, et al. “Efficacy of a therapeutic cocaine vaccine in rodent models,” *Nature Medicine* 2 (1996): 1129–32. Available at <http://www.nature.com/nm/journal/v2/n10/abs/nm1096-1129.html>.
- 2 Thomas Kosten and S. Michael Owens, “Immunotherapy for the treatment of drug abuse,” *Pharmacology and Therapeutics* 108.1 (2005): 76–85. Available at http://www.sciencedirect.com/science?_ob=ArticleURL&_udi=B6TBG-4GMGW53-1&_user=10&_rdoc=1&_fmt=&_orig=search&_sort=d&view=c&_acct=C000050221&_version=1&_urlVersion=0&_userid=10&md5=659bc0b778788646614ccc7e9788a09b.
- 3 The NIH operates the website to track clinical trials in the United States and 150 other countries. See <http://clinicaltrials.gov/>.
- 4 Dr. Kosten’s curriculum vitae, including grant information, can be found at <http://www.bcm.edu/psychiatry/?PMID=7342>.
- 5 Information on the various transactions can be found at <http://sec.edgar-online.com/2001/03/20/0000950135-01-000851/Section18.asp>; <http://sec.edgar-online.com/1997/03/31/00/0000950135-97-001528/Section2.asp>; and <http://www.secinfo.com/d14SA9.zAc.d.htm>.
- 6 The NIH lists grant funding at <http://grants.nih.gov/grants/funding/sbirstr96.txt> and <http://grants.nih.gov/grants/funding/sbirstr97.txt>.
- 7 www.celticpharma.com.
- 8 See, for two examples, Dru Stevenson’s article “Libertarian Paternalism” available at http://www.rutgerspolicyjournal.org/journal/vol3issue1currentIssues/Stevenson_Paternalism.pdf or the Center for Cognitive Liberty and Ethics’ report “Threats to Cognitive Liberty: Pharmacotherapy and the Future of the Drug War” available at <http://www.drugpolicy.org/docUploads/Pharmacotherapy2004.pdf>.
- 9 The text is available from http://books.nap.edu/openbook.php?record_id=10876&page=R1.