CellPress

Opinion

Biologic Approaches to Treat Substance-Use Disorders

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In contrast to traditional pharmacodynamic approaches to treat substance-use disorders (SUDs), the use of biologics (vaccines, monoclonal antibodies, and genetically modified enzymes) is based on a pharmacokinetic principle: reduce the amount of (and, ideally, eliminate) abused drug entering the central nervous system (CNS). Preclinical studies indicate that biologics are effective in both facilitating abstinence and preventing relapse to abused substances ranging from nicotine to heroin. While data are still emerging, the results from multiple clinical trials can best be described as mixed. Nonetheless, these clinical studies have already provided important insights using 'first-generation' tools that may inform the development of effective and commercially viable biologics to treat tobacco-, cocaine-, and methamphetamine-use disorders.

Trends

Biologics reduce the amount of abused drug entering the CNS.

Data emerging from clinical trials with 'first-generation' vaccines are 'mixed'.

Novel adjuvants and hapten redesign are strategies that may improve vaccine efficacy.

A nicotine vaccine incorporating these strategies is currently in clinical trials.

An antimethamphetamine mAb and bioengineered esterases are in clinical development.

Pharmacological Treatment of Substance-Use Disorders

Target-based, small-molecule approaches have not yet yielded highly effective medications to treat SUDs. Thus, there are no pharmacotherapies approved by the US FDA that address cocaine-, methamphetamine-, or cannabis-use disorders. Moreover, based on current trial listings[i], it is unlikely that any medication to treat these SUDs will be approved in the next 5–7 years. Although there are medications approved to treat other SUDs, these are far from ideal. For example, the long-term (52-week) abstinence rates of approved smoking cessation medications (nicotine replacement therapies, bupropion, and varenicline) are generally <20% [1], and substitution therapies (methadone and buprenorphine) remain the most widely used medications to treat opiate-use disorders.

While multiple factors contribute to the dearth of pharmacotherapies to treat SUDs [2], both the inability to develop highly effective, innovative therapies using target-based approaches and advances in immunology and molecular biology have rekindled [3,4] interest in treating SUDs with biologics, including vaccines, monoclonal antibodies (mAbs), and enzymes.

Biologic approaches are grounded on a common pharmacokinetic principle: reducing the amount of (and, ideally, eliminating) abused substance from reaching its target organ, the CNS. Three different approaches have now been explored in clinical trials: (i) vaccines that stimulate the production of antibodies directed against a drug of abuse; (ii) mAbs that bind a drug of abuse; and (iii) genetically modified enzymes that accelerate the metabolism of abused drugs (e.g., the hydrolysis of cocaine).

Mixed Signals Emerge From 'First-Generation' Vaccine Trials

Positive signals have emerged from proof-of-principle trials with two different nicotine vaccines [5,6] and a cocaine vaccine [7,8]. However, these signals manifested only in subpopulations of patients who developed relatively high titers of antidrug antibodies following multiple vaccinations. For example, in a double-blind, placebo-controlled trial of CYT002-NicQb® vaccine [5], subjects received five monthly injections of either active vaccine or placebo. Those subjects with

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the highest tertile of antibody levels exhibited significantly higher rates of abstinence (this is currently the only FDA-acceptable endpoint for smoking cessation and illicit drugs [1,9]) between months 2 and 6 compared with placebo (56.6% versus 31.3%). However, the abstinence rate of subjects in the 'low to mid' antibody range did not separate from placebo. At 52 weeks, the difference in abstinence rates between subjects receiving placebo and those individuals in the highest tertile of antibody responses remained statistically significant (20.2%, $P = 0.012$). Similar outcomes were observed in a double-blind, placebo-controlled Phase II trial with a second nicotine vaccine, NicVAX® [6]. In this study, subjects were injected either four or five times over the first 6 months of the trial with two different doses of vaccine. Subjects with the highest tertile of antibodies had a significantly higher level of sustained (8 weeks) abstinence at 6 months compared with placebo (24.6% versus 12%, $P = 0.024$). A higher abstinence rate was maintained in this group compared with placebo at 12 months (Figure 1). Moreover, in subjects who received five injections of a high dose of vaccine, significantly higher rates of smoking cessation and long-term abstinence were observed compared with the low antibody and placebo arms. Thus, an intent-to-treat analysis (not stratified by antibody levels) of this high dose (400 μg) arm had a significantly higher abstinence rate at 6 and 12 months versus placebo ($P = 0.025$ and $P = 0.038$, respectively), while the abstinence rate of the group receiving the lower dose (200 μg) approached statistical significance at both 6 and 12 months compared with placebo ($P = 0.054$ and $P = 0.056$, respectively) [6]. Based on an apparent dose-related signal, two Phase III trials used a modified vaccination regimen (six injections spaced over 26 weeks) with the high dose of NicVAX® [10]; both trials failed to separate from placebo, with identical end-of-study abstinence rates of approximately 11%.

Small molecules, such as nicotine, cocaine, and heroin, are not inherently antigenic, and must be chemically modified to enable covalent linkage to a protein. Such structural modification may interfere with the ability of the immune system to recognize (and mount an effective immune response to) the abused drug. This issue emerges in the study by Martell *et al.* [7] evaluating a cocaine vaccine (succinylnorcocaine linked to a recombinant cholera toxin B-subunit protein) in cocaine-dependent, methadone-maintained patients. Five vaccinations were administered over a 12-week period (total trial length, 20 weeks). While robust antibody titers to cholera toxin B were detected in every patient, serum antibody levels [defined by the authors as serum immunoglobulin (Ig)-G anticocaine antibody levels of $\geq$43 μg/ml] sufficient to marginally affect cocaine use [an increase in cocaine-free urine samples (45%) compared with vehicle (35%) during trial weeks 9–16] were present in far fewer than half of the patients [7,8]. A second, larger trial in cocaine-dependent patients resulted in modest, albeit nonsignificant, signals of reduced cocaine use in patients with high serum antibody levels [11].

Perhaps more problematic to the development of highly effective vaccines is the challenge created by presenting the immune system with a large quantity (generally in the range of 1–100 mg) of abused drug that must be neutralized in a timeframe of seconds to minutes to effectively reduce entry to the CNS. From both a quantitative and temporal perspective, these demands are greater than those placed on vaccines developed against infectious agents (e.g., a measles vaccine). This is illustrated in a small study of smokers who received four monthly injections of high-dose NicVAX® (400 μg). In these individuals, an intravenous bolus of nicotine (1.5 mg, approximately 1.5 cigarettes smoked) resulted in a modest (12.5%) reduction in single-photon emission computed tomography (SPECT) ligand binding to β2*-nicotinic acetylcholine receptors (nAChRs), corresponding to an approximately 25% reduction in brain nicotine levels [12]. These proof-of-principle trials illustrate the challenges of 'first-generation' vaccines that must be resolved to demonstrate the clinical efficacy necessary for both regulatory approval and successful commercialization.

Improving 'First-Generation' Vaccines

Clearly, it would not be feasible to develop commercially viable 'antiaddiction' vaccines that require frequent, multiple boosts and raise effective antibody levels in only a subpopulation of