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Next-generation vaccines for substance use disorders

Substance use disorders (SUDs) impact an estimated 300 million people worldwide, significantly impairing both health and social functioning. These disorders are marked by an inability to regulate substance use, despite the harmful consequences. Addiction affects various neurotransmitter systems, including dopamine, serotonin, γ-aminobutyric acid (GABA), and glutamate, each of which plays a role in the reward, stress, and self-control pathways of the brain (Koob & Volkow, 2016). While significant advances have been made in neuroscience, our understanding of how these neurotransmitter systems interact and contribute to addiction is still evolving. This knowledge gap represents a significant challenge in the formulation of effective treatments for SUDs. At present, the US Food and Drug Administration (FDA) has approved pharmacological treatments for alcohol, nicotine, and opioid use disorders (Vasiliu, 2022); however, no such treatments have been authorized for SUDs in general, or specifically for stimulant use disorders, such as cocaine and methamphetamine addiction. Notably, the FDA has not approved any new drugs for SUD treatment in the past 40 years.

Given the limited efficacy and challenges associated with current pharmacological treatments, alternative strategies, including immunotherapies like vaccines, monoclonal antibodies, and catalytic enzymes, are gaining interest as potential options for both preventing and treating SUDs (Hossain et al., 2022). Vaccine-based immunotherapies, in particular, have emerged as a promising new avenue for effectively addressing SUDs (Malik & Agrewala, 2023; Vasiliu, 2022). These vaccines differ fundamentally from traditional pharmacological treatments, aiming to elicit an immune response against the substance of abuse to produce neutralizing antibodies rather than altering brain chemistry or neurotransmitter systems directly, and do not require an in-depth understanding of substance-pharmacological receptor interactions. By generating antibodies that bind to drug molecules in the bloodstream, preventing their passage across the blood-brain barrier due to the large size of the drug-antibody immune complex, vaccine-based therapies block the rewarding effects of the substance, thereby reducing reinforcement and aiding in addiction recovery (Bremer & Janda, 2017). Moreover, unlike pharmacological agents, vaccines have the potential to offer long-term protection against substance use with minimal doses.

The development of vaccines for SUDs spans over five decades, with significant progress achieved in the last twenty years. Achieving high vaccine efficacy hinges on the production of high levels of antibodies targeting the substance of abuse. One of the primary difficulties in the development of vaccines for SUDs lies in the inherent challenge of eliciting an immune response to small molecules, known as haptens, which the immune system typically fails to recognize as foreign due to their size. To address this, small-molecule substances of abuse can be conjugated with larger carrier proteins, forming a complex large enough for immune recognition, with the carrier protein serving to signal the immune system towards the attached hapten (Figure 1A). Furthermore, the process of developing vaccines for SUDs involves complex and precise selection and optimization of multiple components to ensure their efficacy and specificity, as discussed in the Supplementary Materials.

While traditional SUD vaccines utilizing protein carriers have shown promise in animal studies, they have encountered substantial difficulties in advancing to clinical trials. For instance, vaccines targeting nicotine and cocaine progressed to Phase 3 trials but failed to emerge as effective treatment options, primarily due to variability in antibody responses among trial participants. Despite over two decades of exploration, the use of protein-based carriers continues to present distinct challenges, as detailed in the Supplementary Materials.

Recent advancements in vaccine research have been inspired by the natural immune response mechanisms observed in viruses and bacteria. These pathogens display a well-organized, repetitive array of antigens on their surfaces, effectively inducing the clustering of antigen receptors on B cells. This observation has given rise to the hypothesis that organizing antigen subunits in a structured and orderly manner on surfaces may substantially increase their immunogenicity (Liu & Irvine, 2015). The concept of multivalency in antigen arrangement, along with improved immune cell recognition and antigen incorporation, is under investigation to strengthen humoral immunity.

Herein, we propose a biomimetic hapten-carrier-adjuvant-integrated molecular vaccine strategy for the development of next-generation SUD vaccines (Figure 1B). This approach utilizes polymers as carriers for hapten conjugation, offering a novel alternative to conventional protein-based carriers. Polymer carriers exhibit several distinct advantages over their protein counterparts, including tunable physical and chemical properties for customized drug delivery systems and a greater capacity for the incorporation of a wide range of substances (Hossain et al., 2020). Additionally, polymer carriers demonstrate superior stability, reduced degradation, extended

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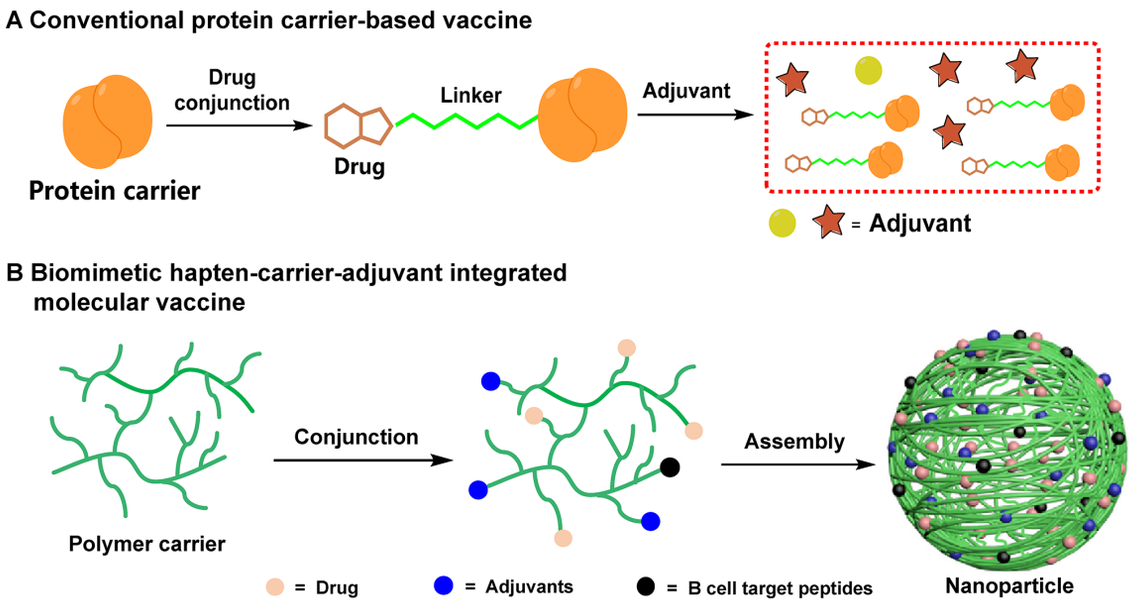

Figure 1 Graphic illustrations of conventional protein carrier-based vaccine and biomimetic hapten-carrier-adjuvant-integrated molecular vaccine

vaccine shelf life, and relatively simple production and manufacturing processes. Moreover, polymers are generally associated with reduced risks of biological contamination, a significant consideration in vaccine safety, with lower immunogenicity compared to protein carriers. To leverage this advantage, molecular adjuvants are covalently conjugated to polymer carriers, rather than being mixed physically, ensuring that they work together in a cohesive and integrated manner to produce a synergistic effect, enhancing overall vaccine efficacy. By combining these elements, polymer-based vaccines for SUDs could offer improved performance, stability, and safety.

In vaccine development, precise control over hapten density is achieved by conjugating haptens and adjuvants, such as toll-like receptor (TLR) and stimulator of interferon gene (STING) agonists, to self-adjuvanting polymers, thereby enabling effective immune responses. This strategy relies on the spatial organization of haptens and adjuvants to optimize immune system interactions, markedly enhancing antigen presentation to antigen-presenting cells (Liu & Irvine, 2015). Adjusting polymer carrier properties, such as charge and hydrophilicity, facilitates the formation of virus-like nanoparticles, exposing haptens and adjuvants on the surface for efficient immune recognition. These nanoparticles can be size optimized for targeting lymph nodes, where B cells, pivotal in antibody production, are preferentially activated. Conjugating B cell-targeting peptides further improves hapten recognition, increasing vaccine efficacy and safety by minimizing off-target effects. Moreover, the use of dynamic hydrogels as antigen reservoirs ensures controlled release and sustained immune activation for durable, high-quality antibody responses. This versatile approach also supports the development of polyvalent vaccines against multiple SUDs.

Next-generation vaccines for SUDs are designed to effectively block the effects of drugs through an induced immunological response. However, there is a potential risk that individuals may increase their drug intake to counteract these blocking effects, thereby elevating the risk of overdose. Concerns about adverse reactions at the injection site, alongside broader issues such as vaccine effectiveness, ethical implications, and access disparities, require thorough scrutiny for a comprehensive evaluation.

SUPPLEMENTARY DATA

Supplementary data to this article can be found online.

COMPETING INTERESTS

The authors declare that they have no competing interests.

AUTHOR'S CONTRIBUTIONS

K.W. and H.W. wrote the original draft and drew the figure. X.W. wrote and edited the manuscript. All authors read and approved the final version of the manuscript.

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