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## New vaccine development for chronic brain disease

The discovery of prophylactic vaccines to protect children from life-threatening infectious diseases was an extremely successful accomplishment of the twentieth century, resulting in 31 vaccines in use today. At the dawn of the twenty-first century, vaccines effective for treatment of established chronic diseases are now under investigation, building on the basic science that has identified molecules that participate in the disease process. Excitingly, progress is being made in exploiting antibody-based therapies against chronic brain disorders that represent a major public health burden.

Both passive and active immunization strategies show promise in the treatment of two classes of chronic brain disease, Alzheimer's disease, and addiction. Active immunization is the traditional approach to systemically administer a drug or molecule of interest to generate an intended antibody response in patients. Passive immunization involves the administration of an antibody generated in a host or model system, which is maximized for efficacy before administration to a patient. Active immunization with A$\beta$ or passive immunization with anti-A$\beta$ antibodies, for example, dramatically reduced amyloid burden and ameliorated behavioral deficits in a transgenic mouse model of Alzheimer's disease ($\beta$-amyloid mice) (Kayed and Jackson, 2009). Similarly, active and passive approaches to vaccinate against cocaine, nicotine, morphine, and methamphetamine indicate reductions in their behavioral and neurochemical effects in animal models (Orson *et al*, 2008). Despite adverse events such as encephalitis observed in clinical trials of amyloid vaccines, as well as variable antibody levels and short duration of action for these vaccines, the preclinical data continue to spur efforts to overcome remaining challenges and develop human vaccines for chronic brain diseases.

The molecule targeted for antibody development, the delivery system and formulation, and the maintenance of antibody response are some of the key variables in the pursuit of safe and effective immunotherapy for chronic brain disease. To date, the primary molecules of interest in Alzheimer's disease have been the pathological hallmarks of the disease A$\beta$ and $\tau$ (self-antigens), aggregation of which is widely believed to be downstream of A$\beta$ deposition (Kayed and Jackson, 2009), although the drug molecules (foreign antigens) are of interest for addiction (Orson *et al*, 2008). These small molecules or peptides are generally poor immunogens and must be tethered to a carrier protein with the goal to stimulate antibodies with high specificity, but to minimize tolerance and adaptive immunity (for example, virus-like particles; Chackerian *et al*, 2006). Adjuvants are also used to enhance the immune response. Few adjuvants are currently approved for use in humans, but new adjuvants in advanced development may help boost the immune response, particularly induction of antibodies, and therefore their efficacy in Alzheimer's, addiction, and other chronic brain diseases (Reed *et al*, 2009).

The maintenance of an adequate antibody response in vaccines is a critical hurdle. Multiple doses of the vaccines have been used to maintain sufficient (normally high) antibody levels in blood to overcome short-term activity; however, the issue of immune tolerance lingers and may explain, in part, the highly variable antibody responses seen in vaccinees. An interesting question that remains to be adequately addressed is the biological activity of the antibodies. Studies of immune responses against infectious diseases have shown that that the biological activity, rather than the antibody level, is more relevant to ultimate vaccine-induced immunity (see Gromowski and Barrett (2007), for an example). It remains to be seen whether the same is true for immunity induced by vaccines developed for Alzheimer's disease, addictions, and other chronic brain disorders.

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