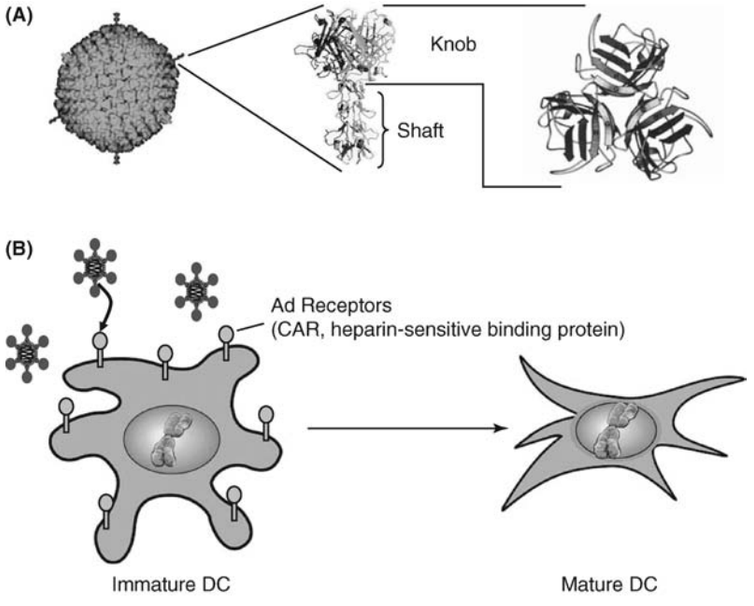


**Figure 1** Structure of the Ad shaft and interaction with putative receptors on DC that facilitate gene delivery and subsequent antigen presentation to stimulate adaptive immunity. (**A**) Location and structure of the viral shaft on the adenovirus particle. (**B**) Schematic representation of the interaction of the Ad fiber with a putative receptor on immature DC that facilitates gene delivery and subsequent differentiation and enhanced antigen presentation. *Abbreviations*: Ad, adenovirus; DC, dendritic cell.

Finally, most Ad vectors exploited for vaccine development to date have been non-replicating, engineered with a deletion in the E1 region genes necessary for viral replication. This feature enhances the safety of the vector, but has other consequences, such as the high doses necessary to elicit potent immunity. An alternative is the use of replication-competent Ad vectors. Wild-type replicating Ad4 and Ad7 have a long history of safe use in the U.S. military and provide the basis for pursuing this approach. Recently, replication-competent Ad vectors have shown promise in the HIV vaccine field (21,22) Although they have not been developed to the extent of replication-defective vectors, which are currently in phase IIb clinical trials (23,24), they are being advanced to human phase I studies. Some of the most effective vaccines to date have been based on live attenuated, replicating organisms. Examples include not only Ad, but also vaccines against smallpox, rabies, anthrax, Bacille Calmette-Guérin, yellow fever, poliovirus, measles, varicella, rotavirus, and rubella (25). Important issues for replication-competent Ad vectors remain those of safety, dependent in part on the route of immunization, and immunogenicity in humans. In this chapter, we will summarize the advantages and disadvantages of replicating and non-replicating Ad vectors and present the current state of the field.

## REPLICATION-COMPETENT rAd VECTORS FOR VACCINES

Replication-competent Ad-recombinant vaccines have an established record of efficacy and safety in humans on the basis of wild-type Ad4 and Ad7 vaccines. Because they are replication-competent and there is limited preexisting immunity to Ad4 and Ad7 in the population, relatively low doses elicit protective immune responses. Studies in nonhuman primates have shown that replicating rAds elicit sustained and potent immune responses that confer protective efficacy in lentiviral challenge models.

The immunogenicity of live, replicating vaccines must always be weighed against safety considerations. For replication-competent Ad-recombinants, the prototype Ad4 and Ad7 wild-type vaccines, routinely administered to military recruits from 1971 to 1996 (26) provide a strong safety record. These live, oral vaccines, safely administered to over 10 million people, were highly effective in controlling acute respiratory disease in the military setting. The vaccines were fully licensed, but never recommended for general use as a civilian need was not documented. Following cessation of production of Ad4 and Ad7 vaccines in 1996, outbreaks of Ad4- and Ad7-induced acute respiratory disease reappeared in the barracks setting, and the need for resuming the military vaccination program became apparent. Currently, manufacture of new vaccine lots is underway.

A key safety feature of the replicating wild-type Ad4 and Ad7 vaccines is their formulation for oral delivery as enteric-coated capsules. The enteric coating prevents dissolution of the capsule in the acid environment of the stomach, and allows delivery to the intestine, where the capsule disintegrates in the neutral pH environment. The oral delivery allows the vaccine to bypass the upper respiratory tract, thus preventing disease. Nevertheless, the vaccine virus causes an enteric infection that is immunogenic and highly effective. Further, the lyophilized virus within the capsule provides a stable, easily stored product. Vaccine administration is readily accomplished, with no needles or special equipment required.

The intranasal administration route has been explored for vaccines intended to elicit mucosal immunity (27). Studies in chimpanzees have suggested that an intranasal replication-competent Ad-recombinant vaccine might be more immunogenic and efficacious than an oral one (28). However, this route is associated with greater safety concerns. Following high-dose ($10^{10}$ viral particles) intranasal administration to mice of a replication-defective Ad, virus was detected in the olfactory bulb (29). Natural Ad infections transmitted via the upper