



TECHNOLOGY

Herpes simplex virus (HSV) infections can cause significant clinical problems and even death in individuals who are immunodeficient or suffering from disorders of skin integrity. Approximately 80% of adults in the United States are infected with HSV, of whom 50 to 60 million are infected with HSV-2. HSV-2 is now the leading cause of genital ulcer disease, and genital HSV-2 infection triples the risk for sexually acquiring HIV infection. Currently, no medication can prevent primary HSV infections or decrease the incidence of recurrences. Thus, there is a huge demand for a safe and effective HSV vaccine.

During the past decade, many studies have focused on the development of various HSV replication-defective viruses and neuroattenuated mutants as potential vaccines against HSV infection. However, the ability of these recombinants to establish lifelong latent infection and to co-replicate with wild-type HSV raises a critical concern for the use of these recombinants in humans, especially as a therapeutic vaccine in individuals who have been latently infected with HSV. Aiming to significantly increase the safety of HSV recombinant viral vaccines while retaining the capability of expressing a broad array of viral gene products, using the T-RExTM (Invitrogen, CA) gene switch technology developed by Dr. Yao and the dominant-negative mutant polypeptide of HSV-1 origin binding protein UL9, Dr. Yao constructed a novel class of HSV-1 recombinants (U.S. patent, 6,251,640 B1) with key features of being replication defective, and capable of inhibiting wild-type HSV-1 and HSV-2 infections (dominant-negative). CJ9-gD is a prototype of the dominant-negative and replication-defective HSV-1 recombinant viral vaccine that expresses high-levels of HSV-1 major antigen glycoprotein D (gD) independent of HSV viral DNA replication. CJ9-gD cannot establish latent infection in vivo and elicits strong and long-lasting HSV-specific neutralizing Ab as well as CD4⁺ and CD8⁺ T-cell responses at levels comparable to those induced in wild-type HSV-1-immunized mice. Immunization with CJ9-gD elicits strong and effective protective immune response against HSV-1 infection in both mouse and guinea pig models of HSV-1 infections. Given these favorable safety and immunological profiles of CJ9-gD and aiming to maximize levels of gD2 expression, Dr. Yao has recently constructed a dominant-negative and replication-defective HSV-2 recombinant (CJ2-gD2), which expresses gD2 as efficient as wild-type HSV-2 infection, and can exert a powerful trans-inhibitory effect on the replication of wild type HSV-2 in co-infected cells. CJ2-gD2 is a more effective vaccine than CJ9-gD in protection against wild-type HSV-2 genital infection and disease as well as reduction of latent infection by the challenge wild-type HSV-2 in sensory ganglia. Furthermore, intracerebral injection of high dose of CJ2-gD2 causes no mortality and morbidity in mice. Collectively, given these demonstrated preclinical immunogenicity and its unique safety profiles, CJ2-gD2 possess unique advantages over any previously described vaccine candidate in prevention against HSV-2 genital infection and disease.

Key features of CJ2-gD: Replication-defective and trans-dominant-negative; Avirulent and incapable of establishment of latent infection; Immediate early overexpression of primary immunogen gD2; Able to achieve high production titer through use of novel tetracycline repressor gene switch technology; and ICP0 knock-out reduces cytotoxicity and major cytokine evasion mechanism.