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Vaccines against HSV-2 and HSV-1 genital herpes: Lessons from the cotton rat model

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In spite of the high health burden of genital herpes, there is still no effective intervention against the disease. The significant gap in knowledge on genital herpes pathogenesis has been further highlighted by the recent failure of GSK HSV-2 glycoprotein D vaccine Simplirix™ (gD/AS04) to protect humans against HSV-2 and the surprising finding that the vaccine protected against HSV-1 genital herpes instead. Our recent work using the cotton rat model demonstrated that gD/AS04 has higher efficacy against HSV-1 compared to HSV-2 genital herpes in cotton rats as well. Severity of HSV-1 genital herpes was less compared to HSV-2 in cotton rats, yet the model allowed for comparative evaluation of gD/AS04 immunogenicity and efficacy. Cotton rats were intramuscularly vaccinated using a prime boost strategy with gD/AS04 (Simplirix™ vaccine), hepatitis B vaccine FENDrix™(adjuvant control), or partially (or completely) inactivated HSV-2 virus and subsequently challenged intravaginally with HSV-2 or HSV-1. gD/AS04 vaccine was immunogenic in cotton rats, induced serum IgG directed against gD-2 and serum HSV-2 neutralizing antibodies, but failed to efficiently protect against HSV-2 disease or to decrease HSV-2 viral load. However, gD/AS04 significantly reduced vaginal titers of HSV-1 and better protected animals against HSV-1 compared to HSV-2 genital disease. The latter finding is generally consistent with the clinical outcome of Herpevac trial of Simplirix™. Passive transfer of serum from gD/AS04-immunized cotton rats also conferred stronger protection against HSV-1 genital disease. These findings suggest the need for alternative vaccine strategies and the identification of new correlates of protection.

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