An Adjuvanted HSV-2 Plasmid DNA Vaccine Is Effective for Prophylactic and Therapeutic Use in the Guinea Pig Model of Genital Herpes

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Introduction

Genital herpes remains a significant public health problem worldwide with no effective vaccine. Primary infection is characterized by painful skin or genital lesions and accompanied by the establishment of a lifelong latent infection in the ganglia. Subsequently, periodic viral reactivation results in virus return to the periphery and recurrent disease or asymptomatic shedding of virus into the genital tract. Virus shedding in the absence of symptoms is believed to be a major source of transmission. There is increasing evidence that a successful vaccine will need to elicit both humoral and cell mediated immunity.

Plasmid DNA vaccines are a powerful approach as they have been shown to elicit both cellular and humoral immune responses. HSV-2 glycoprotein D (gD2) is known to be highly immunogenic and has been used in a number of vaccine formulations. HSV-2 tegument genes encoded by UL46 and UL47 genes have been identified as potent inducers of immunodominant CD8+ T-cells. Here, we present studies examining the impact of novel, codon-optimized plasmid DNA vaccines encoding HSV-2 gD2, UL46 and UL47, with the cationic lipid-based adjuvant Vaxfectin for the prevention and control of genital herpes in the guinea pig model of disease.

Materials and Methods

Animals: Female Hartley guinea pigs (250-300g) were housed in an AAALAC approved vivarium and all studies approved by the UTMB Institutional Animal Care and Use Committee.

Vaccines: Plasmid DNAs containing full length gD2, UL46 and UL47 gene sequences were formulated with Vaxfectin®. For all studies animals were vaccinated 3 times at 2 week intervals with 600 µg pDNA.

Study Design—Prophylactic immunization: Guinea pigs (n=15/group) were intramuscularly vaccinated with either Vaxfectin®-gD2/UL46/UL47 (group 1), Vaxfectin®-gD2 (group 2) or received saline (group 3). Animals were challenged intravaginally with 6.0 log10 pfu HSV-2 strain MS and evaluated daily for primary (D1-14) and recurrent disease (D15-63). Vaginal swabs were collected on days 1, 3, 5, and 7 to evaluate primary HSV-2 replication in the vaginal mucosa and dorsal root ganglia (DRG) were collected at the end of the study to determine latent viral burden.

Study Design—Therapeutic immunization: Guinea pigs intravaginally inoculated with 6.0 log10 pfu HSV-2 strain MS were allowed to recover from primary genital disease and randomized for vaccination with Vaxfectin®-pDNAs (n=14-18) or served as controls (n=14-17). Animals were vaccinated 3 times at two week intervals beginning on day 15 post-challenge and monitored daily (D15-63) for recurrent disease. Quantitative PCR (qPCR): HSV-2 DNA was extracted from vaginal swabs samples and DRG by DNeasy 96 Blood and Tissue kit (Qiagen, Valencia, CA). HSV-2 DNA copies were normalized by parallel qPCR of GAPDH to allow for a more accurate comparison of results.

Statistical Analysis: Comparisons between two groups were analyzed with Student’s T-test or Fisher’s exact test as appropriate. Multiple groups were compared using ANOVA with Bonferroni’s correction. All comparisons were two-tailed.