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## Genetically engineered live-attenuated cytomegalovirus (CMV) vaccines improve pregnancy outcome in the guinea-pig model of congenital CMV infection

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### Background

Congenital CMV infection is a major cause of disability in newborns. An effective preconception vaccine is a major public health priority. The guinea-pig cytomegalovirus (GPCMV) model was utilized to evaluate the efficacy of live, attenuated CMV vaccines generated using a bacterial artificial chromosome (BAC) approach.

### Methods

The GPCMV genome was cloned as a BACmid in *E. coli* and used to regenerate a wild-type viral vaccine (wt), and a highly attenuated recombinant vaccine deleted of the gene encoding the dominant T-cell target, *UL83* (pp65). Seronegative animals were immunized with a two-dose series of each vaccine (0- and 3- week schedule), or placebo. Following establishment of pregnancy, dams were challenged with salivary gland-passaged (SG) GPCMV ( $5 \times 10^5$  pfu) in the second trimester, and pregnancy outcomes were compared.

### Results

Vaccinated dams seroconverted to GPCMV antigen. ELISA titers were significantly higher in the wt ( $2.8 \pm 0.3 \log_{10}$ ) compared to the 409 group ( $2.5 \pm 0.2 \log_{10}$ ;  $p < 0.05$ ). Vaccination resulted in highly significant reductions in the magnitude and duration of DNAemia post-SG challenge, and was associated with improved pregnancy outcomes. Among 13 litters in the control group, there were

29 live and 22 dead pups (43% mortality, mean pup weight of 89 g), compared to 45 live and 14 dead pups born to 15 litters in the vaccine group (26% mortality, mean pup weight 106 g;  $p < 0.05$  vs. control). The two vaccines were comparable in reducing GPCMV transmission at the placental and fetal levels.

### Conclusions

Live, attenuated CMV vaccines are effective at preventing congenital infection and disease in the guinea pig model. Of interest, although *UL83* is an effective subunit vaccine in guinea-pigs, immune responses to *UL83* are not essential for fetal protection in the context of a live-virus vaccine. Recombinant CMV vaccines with targeted mutations of pathogenesis or immune evasion genes warrant further consideration in clinical trials.