Cytomegalovirus Vaccine Development

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Abstract: Although infection with human cytomegalovirus (HCMV) is ubiquitous and usually asymptomatic, there are individuals at high risk for serious HCMV disease. These include solid organ and hematopoietic stem cell (HSC) transplant patients, individuals with HIV infection, and the fetus. Since immunity to HCMV ameliorates the severity of disease, there have been efforts made for over 30 years to develop vaccines for use in these high-risk settings. However, in spite of these efforts, no HCMV vaccine appears to be approaching imminent licensure. The

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reasons for the failure to achieve the goal of a licensed HCMV vaccine are complex, but several key problems stand out. First, the host immune correlates of protective immunity are not yet clear. Secondly, the viral proteins that should be included in a HCMV vaccine are uncertain. Third, clinical trials have largely focused on immunocompromised patients, a population that may not be relevant to the problem of protection of the fetus against congenital infection. Fourth, the ultimate target population for HCMV vaccination remains unclear. Finally, and most importantly, there has been insufficient education about the problem of HCMV infection, particularly among women of child-bearing age and in the lay public. This review considers the strategies that have been explored to date in development of HCMV vaccines, and summarizes both active clinical trials as well as novel technologies that merit future consideration toward the goal of prevention of this significant public health problem.

Spectrum of HCMV Disease, Rationale for Vaccine, and Target Population

**Congenital HCMV Infection: A Major Public Health Problem**

The problem of congenital HCMV infection is unquestionably the major driving force behind efforts to develop a HCMV vaccine. In the developed world, HCMV is the most common congenital viral infection (Whitley 1994). Estimates of the prevalence of congenital HCMV infection suggest that between 0.5% and 2% of all newborns in the developed world are infected in utero (Demmler 1996). In the United States alone, this corresponds to approximately 40,000 infected newborn infants born annually with HCMV infection. The concern is particularly acute for HCMV-seronegative women of child-bearing age. Based on recent HCMV incidence estimates, approximately 27,000 new infections are believed to occur among seronegative pregnant women in the United States each year (Colugnati et al. 2007). Approximately 10% of congenitally infected infants have clinically evident disease in the newborn period, including visceral organomegaly, microcephaly with intracranial calcifications, chorioretinitis, and skin lesions including petechiae and purpura. Although the majority of congenitally infected infants appear normal at birth, these children are nonetheless at risk for neurodevelopmental sequelae, in particular sensorineural hearing loss (SNHL). Antiviral therapy in infected newborns with neurologic involvement is of value in ameliorating the severity and progression of SNHL (Kimberlin et al. 2003), but the toxicities of available antiviral agents are of concern, and the benefits of therapy are limited. Therefore, there are few medical interventions currently available to prevent or limit HCMV-induced neurological morbidity in infants, underscoring the urgent need for vaccine development.