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Development of a vaccine against cytomegalovirus infection and disease

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Human cytomegalovirus causes disabling congenital disease in neonates and severe complications in immunocompromised individuals, making it a high priority for vaccine development. A prophylactic vaccine needs to outperform natural immunity and a therapeutic vaccine needs to elicit rapid protective antiviral responses. This review highlights the three major approaches undertaken by vaccine developers—virus-derived, protein subunit, and gene-based approaches. Each approach offers a unique promise for a successful vaccine by eliciting either a broad immune response or inducing neutralizing antibody responses order(s) of magnitudes greater than natural immunity. A vaccine-elicited immunity is anticipated to have the robustness and duration sufficient to overcome cytomegalovirus infection.

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Introduction

Human cytomegalovirus (HCMV) is a beta-herpesvirus, which infects 40–100% of the adult population worldwide [1]. HCMV establishes a life-long latency in myeloid cells of the bone marrow of the host following primary infection and then periodically reactivates, which contributes to its transmission [2]. HCMV has a broad cell tropism [3], which enables a spread of the virus within and among human hosts. Although often asymptomatic in healthy individuals, HCMV infection causes severe disease in immune-deficient settings, such as transplant recipients and AIDS patients. Importantly, HCMV is the leading infectious cause of congenital disease in newborns. The disease burden in children with permanent disabilities attributed to congenital HCMV is estimated at $1.86 billion annually, making HCMV a high priority for vaccine development [4]. Currently there are no commercial HCMV vaccines available, but advances in the understanding of the HCMV antigens targeted by host immunity and the manufacturing capabilities to produce these antigens offer the promise for an effective vaccine. In this review, we will focus on the development of HCMV vaccines using virus-derived, protein subunit, or gene-based approaches.

HCMV disease

HCMV imposes a significant disease burden on public health and is the most frequent infectious cause of congenital disease. In the US, 30 000 infants are born with an active HCMV infection annually, leading to 400 deaths and 5000 permanent disabilities. Congenital HCMV manifests in many forms, including prematurity, intrauterine growth retardation, microcephaly, focal neurologic deficits, and hearing loss [5–7]. Development of a vaccine preventing congenital HCMV is a major public health priority, as identified by the National Vaccine Program Office and the Institute of Medicine of the United States [4,8•].

HCMV is also the most common viral infection in transplant settings, with 20–60% of transplant recipients developing a symptomatic infection [9]. Patients acquire HCMV from reactivation of latent virus or donor-transmitted virus. HCMV is a common cause of impaired graft survival, graft-versus-host disease, and other opportunistic infections such as invasive fungal infections. These patients can also develop life-threatening, multi-organ infectious disease, as the virus disseminates to the lung, liver, pancreas, kidney, stomach, intestine, brain, and parathyroid glands. A vaccine replacing or supplementing antiviral therapy will increase the efficacy and reduce the cost associated with HCMV treatment in transplant settings.

HCMV causes severe disease in AIDS patients, including retinitis, gastrointestinal disease, and encephalitis [10,11]. HCMV reactivation is associated with prolonged hospital and ICU stays of immunocompromised patients [12]. HCMV association with other diseases has been reported, such as inflammatory bowel disease, Alzheimer's disease, new-onset diabetes, hypertension, immunosenescence, and atherosclerosis [13–16]. In particular, evidence suggests a link of HCMV and several human cancers, such as glioblastoma and breast cancer [17–24]. It is possible that HCMV may act as an oncomodulator to deregulate the tumor microenvironment and promote the initiation and

development of tumor cells [25,26]. Nonetheless, it remains elusive whether HCMV is the causative agent or a bystander in these diseases [27]. A vaccine will potentially relieve the health burden and define the role of HCMV in these diseases.

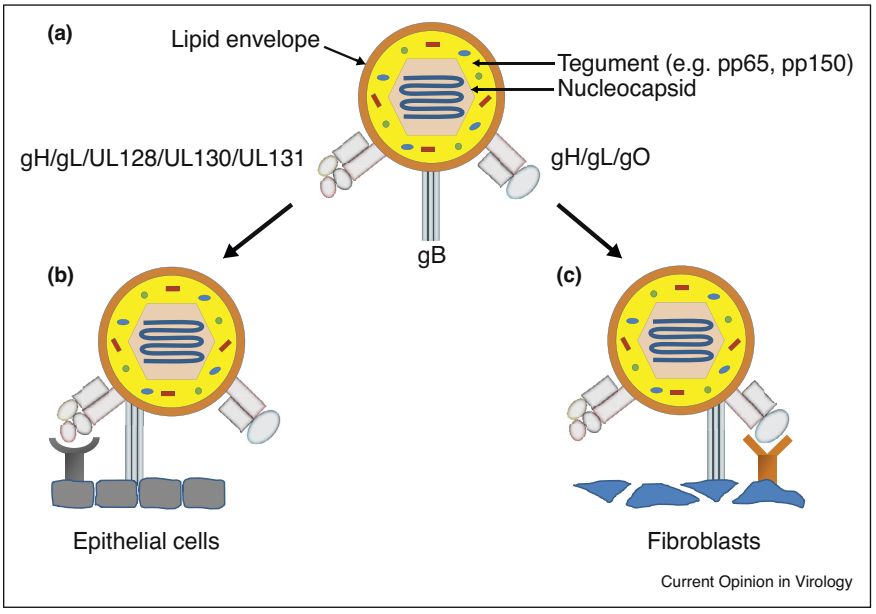
HCMV immune responses

HCMV elicits broad immune responses during primary infection, including innate, humoral, and cellular responses. Despite this, HCMV establishes persistent latency which the host is incapable of resolving, with sporadic reactivation upon loss of immune surveillance. Persistent latency and reactivation are challenging for vaccine development, as a successful vaccine needs to outperform the natural immunity elicited by HCMV. A better understanding of the HCMV-host immunity relationship is crucial to the design and development of a vaccine.

HCMV-specific T cells play a protective role in transplant patients. In bone marrow transplant recipients, a strong correlation is demonstrated between HCMV-specific $CD8^+$ T cell population and disease protection [28–31], and this is further supported by adoptive transplant studies [32–35]. The maintenance of HCMV-specific $CD8^+$ T cells is thought to be dependent on the presence of specific $CD4^+$ T cells. In renal transplant recipients the development of IFNγ $CD4^+$ T cells precedes $CD8^+$ cells in asymptomatic patients, while a lack of $CD4^+$ T cells correlates with CMV disease [36]. A HCMV vaccine targeting transplant settings can benefit from a potent T cell component.

Neutralizing antibody (NAb) responses play an essential role in host protective immunity to HCMV. The rates of congenital infection are markedly reduced in pregnant women with pre-existing HCMV antibodies [37–39]. During primary infection, antibodies are elicited against multiple viral proteins, such as fusion protein gB, entry complex gH/gL/UL128/UL130/UL131 (pentamer), structural tegument proteins (pp65 and pp150), and nonstructural proteins (IE1), but it is pentamer-targeting antibodies that account for >85% of NAbs during natural infection [40•,41•,42•]. The pentamer is required for virus entry into cell types critical to infection and dissemination *in vivo*, such as epithelial cells, endothelial cells, and myeloid cells (Figure 1). It is also required for cell-to-cell spread [43] and transmission of the virus from endothelial cells to leukocytes, a major route of dissemination [44]. Pentamer antibodies block all of these processes *in vitro* [45,46•]. Importantly, serological data support the importance of the pentamer antibodies in the host protective immunity. Antibodies present in seropositive individuals neutralize HCMV in epithelial cells 8–15 fold greater than in fibroblasts, with the pentamer being the key target [47]. Pentamer-specific

Figure 1



The roles of the viral gH/gL/UL128/UL130/UL131 complex (pentamer) and gB in HCMV entry. **(a)** Schematic of HCMV virion including the virally encoded envelope complexes that are responsible for virus entry and are targets of natural antibody responses. **(b)** The pentamer complex is responsible for binding to putative cellular receptor(s) on cell types such as epithelial cells and endothelial cells. **(c)** The gH/gL/gO complex is responsible for binding to a cellular receptor, such as platelet-derived growth factor-α receptor [75], on fibroblasts and trophoblast cells. Once binding to their receptors, these gH/gL-containing complexes are thought to interact with glycoprotein B (gB) which is the primary fusion complex, to induce fusion-mediated virus entry into host cells.