40 Years Is Long Enough!

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(See the major article by Adler et al on pages 1341–8.)

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In 1975, Stanley Plotkin and coworkers developed one of the first live attenuated cytomegalovirus (CMV) vaccines, called Towne 125, which was isolated from a congenitally infected infant and attenuated by cell culture passage and plaque purification [1]. Hundreds of subjects, including renal transplant recipients and healthy men and women, received the early investigational vaccine [2, 3]. The studies showed that the Towne CMV vaccine was safe; induced both humoral immunity, including neutralizing antibody, and cellular immunity, including cytotoxic T cells; and provided protection against CMV disease. However, it fell short in preventing CMV infection when compared to immunity from wild-type virus infection and failed at producing long-term measurable immunity, suggesting it was too attenuated to be effective.

Several live attenuated vaccines are successfully being used for prevention of diseases, including varicella, caused by varicella zoster virus, a herpesvirus cousin of CMV, as well as measles, mumps, and rubella. In addition, the live oral poliovirus vaccine has helped eradicate polio in almost all parts of the world. Why has a successful live CMV vaccine been so elusive?

A nonattenuated, more virulent Toledo strain of CMV was found unsuitable to be a vaccine candidate alone, but, when teamed with Towne as genetically constructed recombinants, 4 Towne/Toledo chimeric live virus next-generation vaccine candidates were produced [4, 5]. In a previous article by Heineman et al, published in a 2006 issue of The Journal of Infectious Diseases, it was shown that these chimeric vaccine candidates were safe in CMV-seropositive subjects, laying the groundwork for the work by Adler et al in this issue, where results of the first phase 1 dose-escalation trial of the 4 chimeras in CMV-seronegative, healthy adult men are reported [5, 6]. All 4 chimeras were safe, well tolerated, and not excreted in bodily fluids, and chimera 4 led the pack as the most immunogenic in producing CMV seroconversion. But more work must be done, because the chimera 4 seroconversions were not robust or long lasting in the lower doses studied, leading future investigators to most likely study higher doses in more subjects to establish the optimal dosage of the leading chimera vaccine candidate. If successful, initial target groups for CMV vaccination might include adolescent girls or young women, to prevent CMV infection during childbearing years [7].

Because of the concerns that a live CMV vaccine may not be immunogenic, may be transmitted to other individuals, may be transmitted from the vaccinated mother to her fetus, may reactivate and cause disease at some point in time, or may exhibit an oncogenic potential and potentiate cancer or other illnesses in vaccine recipients, other approaches to CMV vaccine development have been studied. These approaches, with varying degrees of success, include subunit CMV glycoprotein B (gB) adjuvanted with MF59, which induces neutralizing antibodies; CMV phosphoprotein 65 (pp65) peptide-based vaccines, which induce cytotoxic T-cell vaccines for use in therapeutic vaccination of immune-compromised hosts; canarypox CMV recombinants ALVAC-CMV (gB) and ALVAC-CMV (pp65), which appear to induce neutralizing antibody and cytotoxic T-lymphocyte responses; CMV DNA plasmids containing genes for gB and pp65; and dense bodies containing key CMV immunogenic antigens [3, 8]. However, it is not likely that a single-protein or single-component inactivated CMV vaccine will be a successful vaccine candidate. Therefore, strategies that use multiple components that target different or multiple aspects of the exceedingly complex viral replicative cycle of CMV, such as the gH/gL/UL128/UL130/UL131 pentameric complex compromising 5 viral proteins, should be pursued [9]. Since these proteins appear to be missing from many CMV vaccine strains after multiple laboratory passages, it provides a potential explanation for the modest successes for live CMV vaccine candidates so far studied.

So why do we continue to pursue the elusive CMV vaccine, live virus or otherwise? First, CMV infection is a major yet thus far neglected public health problem, affecting men, women, and children around the world [10]. Congenital CMV infection is the most common congenital viral infection and a leading cause of deafness and vision loss and developmental and motor disabilities. A CMV vaccine to prevent primary infection or reduce
recurrent CMV infections in pregnant women would substantially reduce the burden of congenital CMV disease. Second, prevention of primary CMV infection or suppression of reactivation or reinfection in solid-organ and marrow transplant recipients or individuals with human immunodeficiency virus (HIV) infection, with or without AIDS, or other immune disorders would substantially reduce the CMV disease burden in these vulnerable populations, in whom CMV may cause life- and sight-threatening disease. Finally, a more theoretical but potentially highly significant reason for seeking a vaccine is that CMV has been associated with the development of atherosclerosis, the burden of which a CMV vaccine may some day reduce. The need for a CMV vaccine was so compelling and the results of cost-benefit analyses were so favorable that a CMV vaccine was deemed a high priority by the Institute of Medicine and the National Vaccine Advisory Committee vaccine prioritization reports for the 21st century [11, 12]. Soon thereafter, in 2000, a US government–sponsored meeting proposed activities to support CMV vaccine development, and in 2012, another summit of diverse experts from government agencies, industry, academic and research institutions, public advocacy groups, and professional societies met to address the issues surrounding CMV vaccine development and increase efforts to create a vaccine [13]. So clearly, an effective CMV vaccine is a desirable and, hopefully, attainable goal.

What are the stumbling blocks in our way to a successful CMV vaccine? Despite its ubiquity, CMV remains relatively poorly understood. More studies on the epidemiology, virology, and immunology of CMV infections are still needed to help define correlates of immunity for protection of the placenta and fetus to protect against congenital CMV infection, to expand our limited understanding of the viral antigens important for protective antibodies, and to solve the conundrum of lifelong CMV persistence in apparently immune hosts and the ability of CMV to reinfect individuals with apparent immunity.

If a promising CMV vaccine candidate is identified in successful phase 1/2 trials, how do we efficiently enroll eligible study subjects in large phase 3 efficacy trials? Phase 3 trials evaluating a CMV vaccine for prevention of congenital CMV infection, for example, will need to screen hundreds of thousands of individuals to identify the thousands of CMV-seronegative subjects needed to evaluate the safety and efficacy of the vaccine candidate for prevention of congenital CMV infection and disease. Because CMV infection is relatively common and CMV seroprevalence ranges from 50% to 80% in many populations, a rapid, accurate, cost-effective, and preferably point-of-care serodiagnostics test will be needed to easily screen and identify CMV-seronegative subjects and enroll them in these trials. In addition, a serologic assay that can differentiate reinfection from reactivation would further enhance the knowledge gained from CMV vaccine trials.

CMV also has a so-called image problem. It remains the most common virus most people have never heard of. Public awareness about CMV infection and disease needs improvement. Most individuals have heard of HIV, Ebola virus, or Zika virus, but only one fifth of individuals have heard of the more common CMV [14]. For a CMV vaccine candidate to be accepted, the public will be receiving the vaccine must understand that they would benefit from the vaccine.

Although research of all promising CMV vaccines should continue vigorously, what can be done now to reduce CMV infection in vulnerable populations, such as pregnant women or immune compromised hosts? A popular and practical so-called CMV knowledge vaccine alternative can be used now, especially in pregnant women at risk for acquiring CMV. The components of this preventive measure are CMV awareness and 3 simple hygiene precautions. CMV is transmitted through close contact with body secretions, including saliva and urine. Toddlers and young children often silently shed CMV and may transmit infection to their pregnant mothers. Studies have shown that, through education on hygiene precautions such as careful hand washing after diaper changes, wiping runny noses and mouth drool, avoiding kissing toddlers on or around the mouth, and avoiding sharing food or drink with other children, there is a significant reduction in the risk of CMV transmission and infection [15–17]. Public health officials support these preventive measures, and many states (eg, Utah, Texas, Hawaii, Connecticut, and Tennessee), frustrated by the lack of CMV awareness in their communities, have now passed CMV education laws to facilitate the dissemination of information about CMV diagnosis and prevention strategies [18, 19].

It is said that good things come to those who wait. The babies affected by congenital CMV, as well as others who also experience the effects of CMV disease, have waited long enough. Let’s hope good things come soon.

Note
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References