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A replication-defective human cytomegalovirus vaccine for prevention of congenital infection

Tong-Ming Fu[1], Dai Wang[1], Daniel C Freed[2], Xi He[2], Fengsheng Li[2], Aimin Tang[2], Kara S Cox[2], Sheri A Dubey[2], Suzanne Cole[2], Muneeswara Babu Medi[3], Yaping Liu[3], Jingyuan Xu[3], Zhi-Qiang Zhang[3], Adam C Finnefrock[3], Liping Song[4], Amy S Espeseth[4], John W Shiver[4] and **Danilo R Casimiro[5]**

[1]Merck Research Laboratories, Merck and Co. Inc., USA
[2]Janssen Research and Development, USA
[3]Plasmon Analytics LLC, Berwyn, USA
[4]Sanofi Pasteur, USA
[5]Aeras, Rockville, USA

Congenital human cytomegalovirus (HCMV) infection is a leading cause of birth-defects in the US; developing a prophylactic vaccine is a high priority for public health. Naturally acquired HCMV immunity in women prior to conception is effective in reducing HCMV transmission to fetus during pregnancy; both humoral and cellular immunity are thought to be important in limiting the transmission. To develop a safe and efficacious candidate, we engineered a live attenuated virus by first restoring expression of viral pentameric complex, a target for potent antiviral antibodies, and then applied a genetic/chemical switch to two proteins essential for viral replication. This design permits viral replication of the vaccine virus, named V160, when a synthetic molecule is present *in vitro*, but alternatively is replication-defective when absent. V160 first-in-human evaluation on safety, tolerability and immunogenicity was completed. V160 was administered at four-dose levels in HCMV seropositive and then seronegative volunteers. The vaccine was well tolerated at all dose levels, and there was no vaccine virus replication detected in any study subject. Vaccination in seronegative subjects elicited neutralizing Abs, as well as cell-mediated immune responses, in the range observed with natural immunity. Additionally, the immune responses have demonstrated many quality attributes analogous to those of natural immunity, such as diverse strain coverage and memory B-cell frequency. V160 is a promising vaccine candidate, and its design was based on current understanding of protection by natural immunity against maternal-fetal transmission. The encouraging phase 1 results support the design goals and further clinical evaluation.

tong-ming_fu@merck.com