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Clinical testing of a novel and promising cmv-Vectored HIV vaccine

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Abstract

Despite nearly four decades of research and 35 million deaths worldwide, an effective HIV vaccine remains lacking. In phase-3 testing, candidate vaccines thus far have elicited immune responses that are too narrowly targeted to offer meaningful protection from infection following exposure to circulating strains. Extreme viral diversity and the rapid establishment of latency represent serious challenges to the development of an effective vaccine. Recent pre-clinical studies in non-human primates using an attenuated cytomegalovirus containing an inserts encoding SIV gag rev/nef/tat, pol and env yield CD8+ effector T cell responses that are robust, highly durable, restricted by unconventional antigen presentation mechanisms, and target common insert epitopes in all experimental animals despite a heterogeneous MHC background (i.e., supertopes). These immune responses are mediated by circulating and pre-positioned, tissueresident, effector-differentiated CD8+ T cells capable of response immediately following challenge, without the delay associated with clonal expansion from the central memory population. This immunological profile is ideally suited to cope with the unique challenge of lentiviral infection, and the vaccine construct has now been shown to consistently abrogate early SIV infection following repeated low-dose in approximately 55% of vaccinated rhesus macaques. Plans for phase-1 testing are underway to establish safety and dose-response in humans, and to determine whether the unique immune responses associated with protection will be observed in humans. Study implementation must take into account important considerations regarding appropriate selection of participants, pre-existing immunity to CMV, use of a live-attenuated viral vaccine, and must employ an optimally informative study design. Keywords: HIV, vaccine, CMV, cellular immunity, phase-1 testing, safety, immunogenicity.

Novel serotype Ad vectors

Ads are double-stranded DNA viruses that have a characteristic genomic and physical structure. Replication-incompetent Ad vectors are typically stable and immunogenic and can be produced in large quantities, which makes them attractive as vaccine platforms. Ad vectors have long functioned as key model systems for molecular biology and gene therapy, they have also been explored as candidate vaccines in recent years. Interestingly, the potent immunogenicity of Ad vectors has proven to be a major limitation for gene therapy applications by reducing the duration of transgene expression, but this property has been exploited by the vaccine field and has led to the development of Ad vaccine vectors. Ad vectors from multiple species and serotypes are currently being explored as candidate vaccines for a broad range of infectious pathogens as well as for cancers. Most Ad vector development programmes for HIV-1 have used non-replicating Ad vectors in which the early region 1 (E1) gene, which is essential for virus replication, is deleted; however, replicating Ad vectors are also currently being explored.

Biography

Marcel Curlin received a doctoral degree in medicine from the Oregon Health and Sciences University in 1995. After completing postdoctoral training in Medicine and Infectious Diseases, he pursued research on HIV pathogenesis (University of Washington). From 2010 to 2015, Dr. Curlin served as Chief of HIV/STD laboratory sciences for the US CDC in Bangkok, Thailand. In 2015 he returned to OHSU where he leads phase-1 clinical testing of T-cell based HIV vaccines for the vaccine research program directed by Dr. Louis Picker. Dr. Curlin is clinically active on the Infectious Diseases Inpatient consultation service.

Biography

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