3108 Safety, Maximum Tolerated Dose and Immunogenicity of CMV–MVA–Triplex in Healthy Volunteers with or without Prior Immunity to CMV and Vaccinia

Clinical Allogeneic Transplantation: Conditioning Regimens, Engraftment and Acute Transplant Toxicities
Program: Oral and Poster Abstracts

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In the era of preemptive antiviral therapy, cytomegalovirus (CMV) still remains the cause of major health complications, profound defects in immune reconstitution, and significant morbidity in post–transplant recovery of immune–compromised HCT recipients. Substituting antivirals with a vaccine that harnesses the native immune response to CMV may improve outcomes for HCT recipients.

Modified Vaccinia Ankara (MVA), a vaccinia virus being investigated as a smallpox vaccine by the Defense Department, is a safe and robust delivery system to treat or prevent a wide range of diseases including HIV and cancer. Replication–defective MVA is safe, well tolerated and strongly immunogenic when given to HCT recipients or AIDS patients. We developed a multiple-antigen recombinant MVA with genes encoding 3 immunodominant CMV proteins: UL83 (pp65), UL123 (IE1-exon4), and UL122 (IE2-exon5) (CMV–MVA–Triplex), and established its pre–clinical safety and immunogenicity using humanized HLA transgenic mouse models and human PBMC from CMV–seropositive healthy volunteers and HCT recipients.

Defining safety, persistence of the virus, maximum tolerated dose and immunogenicity of CMV–MVA–Triplex in healthy volunteers is a critical first step in its clinical development for HCT recipients as required by the FDA. In a Phase I trial (NCT01941056), these endpoints were evaluated in 24 healthy volunteers (age: 18–60), with or without prior immunity to CMV and vaccinia. Three escalating dose levels (DL) were administered intramuscularly (DL1=10xE7; DL2=5x10E7; DL3=5x10E8 pfu/dose) in 8 subjects/DL, with a booster injection 28 days later, and follow up for 1 year.
As of July 2015, all 24 planned volunteers were enrolled, vaccinated and followed for at least 4 months. Vaccinations at all DL were well-tolerated, with only a few expected injection reactions and no SAE or dose limiting toxicities. Immunogenicity of the vaccine was evaluated by measuring the levels of the CD137 T-cell surface marker representing functional activation of PBL harvested from vaccinees and stimulated 24 hours with full–length pp65, IE-1 and IE2 overlapping peptide libraries, or direct measurement of CMV-specific T-cells using HLA multimers. CMV-MVA-Triplex induced robust expansion of pp65-, IE1- and IE2–specific CD8 and CD4 T-cells in vaccinated CMV-seropositives, at each DL (Cf. plot showing geometric mean with upper lower/limits of the pp65 T-cell levels for DL2 cohort). HLA multimers identified CMV-specific T-cells whose expansion closely followed CD137–activated CMV-specific T-cells in vaccinees with common HLA alleles which have a corresponding known CMV-CTL epitope (data to be presented).

A statistical analysis performed using generalized estimated equations indicated that the post–vaccination levels of pp65–, IE1– or IE2–specific CD8 and CD4 T-cells were significantly increased, with p-values ranging from $3 \times 10^{-5}$ to 0.025. For example, the pre-/post-vaccination median pp65–reactive CD4$^+$ CD137$^+$ T-cells rose from 1.3 to 4.4 cells/µL (p=$3 \times 10^{-5}$); and pp65–reactive CD8$^+$ CD137$^+$T-cells rose from a median of 0.22 to 3.1 cells/µL (p=0.003). Importantly, robust immunity was detected in CMV-seronegatives (as shown in the plot for UPN 14 and 18), as well as in subjects who had received smallpox vaccinations. Elevated frequencies of CMV–specific CD4 and CD8 T cells for all 3 antigens plateaued after day 56, but in most cases remained elevated up to one year post–vaccination (data to be presented). Circulating MVA vector in blood was assessed by real–time PCR post–injection and showed only minimal residual vector DNA [10–30 gc/mL] in just 2 vaccinees in the DL3 cohort that disappeared within 3 months. These results provide evidence that CMV–seropositive HCT recipients, whether they receive stem cell product from CMV–seropositive or –seronegative donors could respond to CMV–MVA–Triplex by generating protective CMV–specific immunity.

CMV–MVA–Triplex is the first vaccine against CMV that uses a recombinant MVA incorporating multiple CMV antigens, developed for HCT recipients, who are at risk for CMV reactivation. The safety and marked immunogenicity of CMV-MVA-Triplex in this Phase I trial, warrant testing of the vaccine in the HCT setting. A Phase 2 multicenter, placebo–controlled trial to assess CMV-MVA-Triplex in CMV seropositive recipients, receiving HCT from matched related or unrelated donors will start in Fall 2015.

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