CALIFORNIA HIV/AIDS RESEARCH PROGRAM

CMV Immune Modulation Amplifies RhCMV/SIV Vaccine Efficacy

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Recently, a vaccine based on rhesus cytomegalovirus (RhCMV) met with impressive success in protecting rhesus macaques against SIV disease (a disease that is similar to HIV disease in humans). This novel RhCMV-based vaccine induces broad and peculiar immune responses. This application is an attempt to understand why the immune responses stimulated by RhCMV vectors are so effective in stopping SIV.

Cytomegalovirus (CMV) has long been known to exert a profound global effect on the immune system. Only recently it was shown that CMV infection may account for much of the non-heritable immune variation between human individuals. Remarkably, CMV is able to confer new capabilities on certain immune cells: immune cells formerly thought to be incapable of robust "memory" responses become more capable, while other cells thought incapable of making certain receptors make them.

We hypothesize that these immunomodulatory effects of CMV infection contribute to protection against SIV in individuals receiving RhCMV-based SIV vaccines.

We plan to:
1. Determine if SIV-specific CD8+ T cells (a kind of immune cell) in macaques vaccinated with RhCMV/SIV vectors, but not Ad/SIV vectors, express an activating receptor, NKG2C, not usually seen on T cells.

2. Determine if the degree of protection afforded by RhCMV/SIV vectors is positively correlated with expression of NKG2C on SIV-specific CD8+ T cells. Animals vaccinated in part 1, above, will be challenged after vaccination by repeated low-dose SIV exposure.

Expected results:
Our hypothesis predicts that induction of certain uncharacteristic receptors on host T cells will be associated with protection against SIV in individuals receiving RhCMV-based SIV vaccines. If this hypothesis is confirmed, then we will have uncovered a unique and important mechanism that contributes to vaccine efficacy. This understanding will open new avenues in HIV vaccine research.

Additional background:
We do not yet understand the requirements for protective immunity against HIV. Nonetheless, some success has been obtained in protection against SIV by reliance on RhCMV-vectored

vaccines, which provoke strong adaptive immunity to vaccine antigens but also act broadly on innate immune cells. Additionally, it has recently been appreciated that HCMV infection of humans may confer more immunologic variability than the heritable genetic factors that have received so much scientific scrutiny.