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Human Cytomegalovirus-based Therapeutic Vaccine for Human Papillomavirus-induced Cancer

Human Papillomavirus (HPV) is one of the most common sexually transmitted disease worldwide with high prevalence. A recent study showed HPV has a global prevalence of 11.7% in women. HPV is the main cause of cervical cancer in women and HPV-16 (18; 31 and 45 also) genotype are most implicated. HPV-encoded E7 and E6 are the principle conserved oncogenes responsible for cell transformation and carcinogenesis. Despite the presence of prophylactic vaccines, there is no approved therapeutic vaccine for HPV-induced cancer although different strategies have been attempted.

Human cytomegalovirus (HCMV) is a β-herpesvirus that affects 60-80% of population in developed countries. HCMV infection is lifelong in normal healthy patients, causing no disease and remaining mostly in a state called viral latency. Latent HCMV infection produces a pool of HCMV-specific effector/effector memory $CD8^+$ T cells, a type of white blood cell that kills cancer and virally infected cells, occupying up to 10% of the circulating memory compartment, a phenomenon called memory inflation. We intend to use this phenomenon to generate novel vaccines producing high levels of functional effector memory $CD8^+$ T cells against cancer. To mediate their activation and function, $CD8^+$ T cells have to bind a cell surface molecule called major histocompatibility complex (MHC) class I molecules which are expressed on all nucleated cells and play an important role in immune response. These molecules present peptides derived from pathogens to immune effector cells, thus driving not only a lytic response against the infected cells, but also generates memory cells to protect cells from subsequent infections by the same pathogen. HCMV has a set of genes that alters antigen presentation which confers immune evasion and aids in latency establishment. Some unique short (US) proteins (US2, US3, US6, and US11) which are expressed differentially at different stages of the viral infection downregulate MHC-I molecules. This can reduce the recognition of $CD8^+$ T cells to virally infected cells.

In this project, we aim to optimise HCMV vector for best antigen presentation by deletion of MHC-I downregulating genes and hence, better $CD8^+$ T cell response. This modified will be used to express E6/E7 antigens to drive cytotoxic activity of $CD8^+$ T cell against HPV-induced cancer. Humanised mouse model (a mouse model expressing human immune system) will be used test efficiency of our vaccine in vivo.

In order to induce strong $CD8^+$ T cell responses a HCMV vector has been optimised for maximal antigen presentation by deletion of HLA class I downregulating genes (US2-US11) using bacterial artificial chromosome (BAC) technology. This optimised vector will be used to express HPV E6/E7 by inserting the DNA sequence of shuffled E6/E7 that has lost its transforming activity but maintained its immunogenicity. The mutant viruses will be tested in vitro to stimulate E6/E7-specific $CD8^+$ T cells. In the next step, the vaccine candidates with a strong in vitro capacity to stimulate E6/E7-specific $CD8^+$ T cells will be evaluated in a humanised mouse model of cervical cancer. For this purpose immunodeficient mice are reconstituted with human HLA-A2 expressing $CD34^+$ hematopoietic stem cells that have been isolated from human cord blood (60% of Human $CD45^+$ cells). These mice are inoculated with HLA-A2 expressing human cervical cancer cells and subsequently vaccinated with the candidate vectors. The HCMV-specific $CD8^+$ T cell responses that dominate during the acute phase are typified by classical expansion, contraction and formation of long-term central-memory pools ($CD27^+$, $CD28^+$, $CD62L^+$, $CD127^+$ and $IL\text{-}2^+$), whereas inflationary responses display an effector-memory phenotype ($CD27^-$, $CD28^-$, $CD62L^-$, $CD127^-$ and $IL\text{-}2^{+/-}$) will be measured.

Our results will provide the preclinical basis for development of a therapeutic vaccine against cervical cancer.