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Towards mucosal DNA delivery: structural modularity in vaccine platform design

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Hepatitis E virus (HEV) is a feco-orally transmitted, hepatotropic, non-enveloped virus. Insect cell expressed virus-like particles (VLPs) mimic the virus in terms of their stability and integrity in gut environment[1] and at extremes of temperature. Additionally, the tertiary structure of the capsid protein is organized such that extensive modification of the surface-protrusion forming domain (P) does not affect the ability of the dimeric building blocks to assemble into VLPs. These properties make HEV capsid extremely suitable to be modified for use as an orally deliverable vaccine/ theranostic nanoparticle. Genetic engineering or chemical modification of the P domain can be implmented to express foreign peptides or other moieties. This can be achieved without impacting the conformation of the chimeric capsid protein in VLP formation. HEV VLPs expressing p18, predominant antigenic region of the V3 loop, when administered orally in mice, generated a strong immune response1. Chemical modification of key mutated residues allowed the attachment of a breast cancer targeting ligand to the VLP surface, and this modified VLP was trafficked to tumor sites *in vivo* and in cells. The hollow core of the VLP has key positively charged residues that allow for DNA and other charged material to be incorporated through simple disassembly and reassembly. When administered orally into mice, HIV-1 *gag* DNA carried by HEV VLPs induced a strong cell mediated immunity to Gag protein, indicating that the packaged VLP was not only delivered to the immune cells, but was also successful in releasing and expressing the gag DNA with concomitant immune response generation[2]. Thus, HEV VLPs can serve as the adjuvant of the intended DNA vaccines as a delivery system to target mucosa. The presence of the VLP in the vaccine formulation circumnavigates the requirement for an external adjuvant. A variety of therapeutic and diagnostic materials, such as fluorescence tags, electron microscopy dense metals like gold and hyperthermia media can be encapsulated or attached to engineered VLPs that will specifically target an organ or cell type. The insect cell expression system is inexpensive, with a high protein yield. Moreover, HEV antigenicity is limited to the P domain, and we have seen that engineering of the VLP at the P domain completely abrogates binding to HEV specific antibodies[2].

Biography

R Holland Cheng is a professor of Molecular and Cellular Biology at University of California, Davis. His area of expertise is in proteome imaging of model/ macromolecular systems. Dr. Cheng has served as a Panel Reviewer for NIH programmed project grant, NIH Microbiology & Infectious Diseases Research Committee, NIH National Center for Research Resources, Wellcome Trust, UK and Earth & Life Sciences Council, Netherlands (2002). His lab is currently trying to use the knowledge of HEV structure to develop nanoparticles for diagnostic and therapeutic applications.

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