ISID Small Grants Program Final Report

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The neutralizing activity of the prime-boost regimen with rBCG-E12 and rDIs-E12 candidate vaccine

Genetic diversity in HIV-1 is well evidenced from the large number of different HIV-1 strain isolated around the world, which have been divided into three groups. The major group has been further divided into 10 nucleotide sequence defined subtypes. In Thailand, two major subtypes of HIV-1 are prevalent: clade B' (Thai subtype B) in intravenous drug abusers and clade E (Thai subtype A) in heterosexuals.

Most of the candidate vaccines currently in production are based on B clade virus which, although prevalent in the developed countries, is not the clade which is found in most parts of the developing countries. HIV-1 clade B-derived vaccine could hardly prevent infection of clade E virus.

Recombinant live attenuated *Mycobacterium bovis* BCG (BCG) vector-based vaccine targeted to HIV-1 and simian immunodeficiency virus were reported to induce both humoral and cellular immune responses in animal models against a variety of antigens such as Gag, Env and Nef. The BCG immunization is known to generate primary Th1 and delayed-type hypersensitivity responses that are considered to be suitable for a vaccine development for HIV-1.

Recombinant viral vectors are believed to have similarlity to live attenuated vaccines. The expression vector results in antigen processing through the major histocompatibility (MHC) class I pathway, which induces CD8+ CTL. Earlier studies have evaluated the safety and immunogenicity of recombinant vaccinia vector.

The objectives of this study are to construct the new candidate HIV-1 subtypeE vaccine, rBCG-E12 and rDIs-E12 and to develop a prime-boost strategy with the goal of eliciting broadly neutralizing antibodies against HIV-1 to provide sterilizing immunity for this virus.

In the previous study, a research group in NIID, Japan demonstrated that the V3 sequence of 12 amino acids of HIV-1 CRF01-AE (E12 epitope) fused with mycobacterial α-antigen was secreted from BCG cells (rBCG-E12) and could induce NT-Ab against CRF01-AE primary isolates. However, the NT-Ab titer in guinea pig was not enough to obtain protective efficacy. So, we attempted to boost the NT-Ab by rDIs expressing E12 epitope-α-antigen fusion protein (rDIs-E12).

In this study, we have successfully constructed rDIs-E12 candidate vaccines. To clarify the enhancement of HIV-1 specific immune response by the consecutive vaccine regimen using these two vaccine constructs, we have examined E12-specific ELISPOT (cellular immunity) and antibody production in mice.

From the ELISPOT experiments, the prime-boost regimen enhanced effector cell response for alpha antigen but could not enhance that for E12 peptide. Although the V3 epitope in HIV subtype B contains CTL epitope restricted by mouse class I H2d, to our knowledge, there is no report on such CTL epitope in HIV CRF01-AE, and the lack of CTL induction should be ascribed to not matching class I-restriction in the HIV-1 subtype. However, the ELISPOT response against alpha antigen was significantly boosted by rDIs-E12, suggesting that the prime-boost regimen could have an effect for enhancing cellular immunity.

Regarding antibody response, rBCG-E12 immunization induced NT antibody production in guinea pigs and in mice (reported by NIID, Japan). However, the rDIs-E12 boosting could not enhance anti-E12 peptide antibody titer. Taking account of enhancing anti-alpha antigen antibody titer by the same regimen, the antigenicity of E12 peptide inserted in rDIs-E12 was not enough for enhancing anti-E12 antibody, implying that the conformation of E12-alpha antigen fusion protein in rDIs-E12 may be different from that in rBCG-E12.

This grant has contributed to our study for HIV vaccine development in Thailand. We will continuously study for better HIV vaccine development to produce NT antibody by construction and evaluation such prime-boost regimen for the other Env construct of both rBCG and rDIs vector systems. ❖

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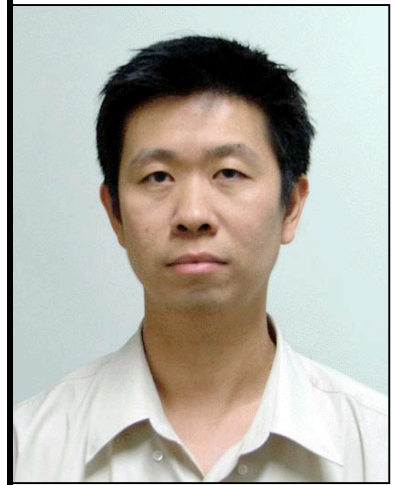
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