HIV-1 integrase (IN) is the enzyme that catalyzes insertion of viral DNA into the genome of host cells. IN is an attractive target of drug discovery for the highly active anti-retroviral therapy (HAART). To date, however, there is only one approved drug, raltegravir (RAL) (Merck), as an IN inhibitor. Although RAL is a potent IN inhibitor, new compounds are required because of the facts that RAL interacts a catalytic domain of IN which easily acquires tolerance and that there is no other approved drug. To date, we have developed new IN inhibitors based on the HIV-1 gene product, Vpr, by screening a library of overlapping peptides, indicating that IN inhibitors might exist in the viral pre-integration complex (PIC). The lead peptide (Ac-EEAIIRILQQLLFIHFRIGENH) was proven to be at the second helix region of Vpr. For acquiring higher IN inhibitory activity, the helix structure of Vpr should be mimicked. In this seminar, we will introduce our results on structure-activity relationship studies of staple peptides derived from the above lead peptide for the development of more potent IN inhibitors. A staple peptide is a peptide in which two separated amino acids are covalently bonded at their side chains. This strategy causes stabilization of an α-helix structure. We have synthesized peptides in which i and i+4 positions of helix peptides are “stapled”, and as the preliminary results, we have elucidated that staple peptides shows more stable helix by CD and that there are some advantages of staple peptides in anti-HIV activity. In these experiments, Ac-EAlgRII-$\text{C}_{\text{QLL}}$FIHFRIG-NH$_2$ (CP-4S, peptide is stapled at $\text{C}_{\text{QLL}}$) was the most potent. We have also studied on the effect of additional hydrophilic sequences, R$_8$ (R = Arg) and (RE)$_4$ (E = Glu). Further studies to develop more active anti-HIV peptides are in progress in our laboratory.