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Preventive and therapeutic AIDS peptide vaccines

In the optimal scenario a preventive AIDS vaccine should eradicate (sterilizing immunity) an initial HIV infection by multiple strains regardless of the route of infection (mucosal or parenteral) and regardless whether the inoculum consists of free virions or of infected cells. Although over 20 AIDS vaccines are underoing clinical trials, to date no preventive vaccine meeting these criteria is on the near horizon [1–4]. Hopes were placed on live attenuated vaccines based on encouraging studies with nef gene deleted SIV in monkeys protecting them from challenge with virulent SIV [5].

However, the stability of non-virulence of defective HIV-1 mutants has still to be guaranteed and if ever used in humans such vaccine will have to include a myriad of attenuated viruses from different subtypes and classes to provide broad cross-protection. Because of the present comlexity of using attenuated HIV live vaccines, attempts were made to use non-HIV live vectors for HIV antigens. A recombinant canary pox virus expressing gp160 MN (ALVAC-HIV) has actually induced potent CTLs albeit only in 39% of vaccinees and only after multiple boosts with soluble rgp160 [6].

We have taken a different approach to HIV-1 vaccines utilizing peptide-carrier conjugates. In principle, once the elements of protective immunity have been defined, relevant synthetic peptide(s) vaccine prototypes can be designed and rapidly and inexpensively modified to address the changing antigenic spectrum of virus mutation. Furthermore, novel technologies allow the coating of peptides with different delivery systems that can protect them from proteolytic digestion, improve passage across mucosal surfaces and target antigen processing along MHC-class I and/or class II pathways. Several groups have recently demonstrated that in vivo priming of CMI with synthetic peptides can be achieved to effectively protect mice against infection.

With regard to HIV-1 related peptide immunizations mixed results have been reported. HIV specific CTL could, for example, be induced in mice with polymeric antigen in the form of hybrid Ty virus like particles (VLP) carrying V3 region epitopes [7]. Multiple-Antigen-Peptide Systems (MAPS) and multiple branched-peptide immunogens have also been utilized for synthetic peptide vaccines for HIV-1 [8, 9] with limited immunogenictiy. The HIV-1_{MN}V3 octameric peptide vaccine in alum adjuvant induced only modest antibody resonses after the third immunization of HIV-1 negative volunteers [9]. In contrast, our single epitope MN-PND-PPD vaccine in submicrogram doses and without adjuvant induced long-lasting high titer antibodies in animals and in HIV uninfected human volunteers. These antibodies recognized PND peptides from the homologous MN-PND peptide, from HIV-1_{SC} and to a lesser extent from RF, NY-5 and CDC-42 [10]. We have also demonstrated in our vaccines the presence of HLA-B7 restricted specific CD8+ and CD4+CTL [10]. HLA-B7 restricted CTL were also reported by Gorse et al in volunteers receiving V3 octameric peptide vaccine [9]. Furthermore, Safrit et al. [11] have reported that CTL clones from acute seroconvertors were also HLA-B7-restricted in the V3 loop and Berzofky et al. [12] observed in HIV-1 positive individuals an HLA-B7 restricted CTL response to the p18 peptide from the V3 loop.

We have experience with the MN-PND-PPD vaccine by designing multi-peptide (multi-epitopic PND, nef, gp41) vaccines conjugated to PPD and to recombinant proteins of M.tuberculolosis such als 10 kDa and 30 kDa. Preliminary studies in guinea pigs and in HIV+ human volunteers demonstrated that *primary isolate* neutralizing antibodies can be generated or augmented by this strategy.

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