Antibody and T cell response to the protease cleavage sites drive extensive mutations and correlated with protection against higher dose of SIVmac239 challenge and disease progression in Cynomolgus macaques

M. Luo[1,2], D. Tang[1], C. Rupert[1], X.-Y. Yuan[1], J.C. Pinto[3], C. Prego[3], M. Alonso[3], C. Barry[1], R. Pilon[4], D. La[1], C. Daniuk[1], J. Tuff[1], S. Pillet[4], T. Bielawny[1], C. Czarnecki[1], P. Lacap[1], G. Wang[4], S. Tyler[4], B. Liang[4], T. Ball[2,4], P. Sandstrom[4], G. Kobinger[2,4], F. Plummer[2,4]
[1]National Microbiology Laboratory, HIV and Human Genetics, Winnipeg, Canada, [2]University of Manitoba, Medical Microbiology, Winnipeg, Canada, [3]Santiago de Compostela, Santiago, Spain, [4]National Microbiology Laboratory, Winnipeg, Canada
Presenting author email: ma_luo@phac-aspc.gc.ca

Background: The protease of HIV-1 is a small 99-amino acid aspartic enzyme that mediates the cleavage of Gag, Gag-Pol and Nef precursor polyproteins. The process is highly specific, temporally regulated and essential for the production of infectious viral particles. A total of twelve proteolytic reactions are required to generate a viable virion. Since the protease cleavage sites of HIV-1 are highly conserved among major subtypes of HIV-1, direct immune responses against these cleavage sites would destroy the virus before its permanent establishment in the host. The vaccine could also force the virus to accumulate mutations around these sites and eliminate the normal function of the HIV protease thus eliminating infectous virions. Therefore a HIV vaccine targeting protease cleavage sites could be effective.

Methods: We have conducted a proof of concept study to investigate the feasibility and effectiveness of this vaccine approach. The recombinant VSV-peptides were used to immunize cynomolgus macaques and nanopackaged peptides were used to boost the immune response to the peptides overlapping the 12 protease cleavage sites of SIVmac239. The immunized macaques and controls were cumulatively challenged intrarectally with increased dosage of SIVmac239. Antibody and T cell responses to the peptides, SIVmac239 infection and plasma viral load, CD4+ and CD8+ T cell counts were monitored.

Results: Antibody and T cell responses to the 12 protease cleavage sites can protect macaques against higher dosage of SIVmac239 intrarectal challenge (p=0.005, R=0.42) and the vaccine group maintains significantly higher CD4+ counts (p=0.0002) than the controls weeks after being infected. Viral sequence analysis detected extensive mutations in the PCS and the flanking region. The break-through viruses of the vaccine group have higher mutation rate in PCS regions than that of the control group. The extensive mutations around PCS sites correlated with lower viral load (P< 0.0001).

Conclusion: A HIV vaccine targeting sequences around the 12 protease cleavage sites can be used to prevent HIV-1 infection and to treat HIV-1 infected patients.