ANNOUNCEMENT OF FINAL ORAL EXAMINATION
FOR THE DEGREE OF DOCTOR OF PHILOSOPHY

CANDIDATE: Suzanne Kijewski

DEPARTMENT OR PROGRAM: Microbiology, Program in Immunology

TITLE OF DISSERTATION: “Mechanistic Differences in Interactions of HIV-1 and HIV-2 with Dendritic Cells”

DATE, TIME, AND PLACE:
Thursday, July 16, 2015 at 10:00a.m.
Boston University School of Medicine
72 E. Concord Street (Room L 504)
Boston, MA 02118

EXAMINING COMMITTEE

FIRST READER: Dr. Suryaram Gummuluru
SECOND READER: Dr. Andrew Henderson

THIRD READER:
CHAIRMAN OF THE EXAMINING COMMITTEE: Dr. Gregory Viglianti Email: gviglianti@bu.edu

ADDITIONAL COMMITTEE MEMBERS:
Dr. William Cruikshank
Dr. Paul Duprex

Members of the committee are asked to confirm attendance by replying directly to the Chairman of the Examining Committee.

ALL MEMBERS OF THE SCHOOL OF MEDICINE FACULTY ARE INVITED TO ATTEND.
MECHANISTIC DIFFERENCES IN INTERACTIONS OF HIV-1 AND HIV-2 WITH DENDRITIC CELLS

SUZANNE DELIGHT GEER KIJEWSKI

Boston University School of Medicine, 2015

Major Professor: Suryaram Gummuluru, Ph.D., Associate Professor of Microbiology

ABSTRACT

Pathogenic mechanisms that account for the dramatic differences between the HIV-1 and HIV-2 epidemics remain unknown. Myeloid dendritic cells (DCs) are sentinels of the immune system, which sense invading pathogens and initiate immune responses. I hypothesize that failure of HIV-2 to overcome DC-intrinsic defense mechanisms results in diminished virus replication and reduced pathogenesis \textit{in vivo}. Recent studies from our laboratory have identified capture of HIV-1 by CD169 (Siglec1), which results in preservation of virus infectivity in peripheral non-lysosomal compartments and transfer to CD4$^+$ T cells, a mechanism of DC-mediated trans infection. HIV-1 interaction with CD169 was dependent on incorporation of a ganglioside, GM3, in the virus particle membrane. We hypothesized that reduced interaction of HIV-2 with CD169 is crucial for its attenuated pathogenic phenotype \textit{in vivo}. Interestingly, HIV-2 virion assembly sites were divergent from HIV-1, which correlated with reduced incorporation of GM3 in HIV-2 virions, and a significant decrease in capture of
HIV-2 compared to HIV-1 by mature DCs. Furthermore, reduced CD169-dependent HIV-2 capture by DCs attenuated access of HIV-2 to DC-mediated trans infection. In contrast to the trans infection pathway, HIV-2 could establish productive infection in DCs, though productive infection of DCs by HIV-2 resulted in innate immune activation, induction of IFN-α production and attenuated spread of virus in DC – CD4⁺ T cell co-cultures. As opposed to HIV-2, productive infection of DCs by HIV-1 was attenuated and failed to trigger type I IFN responses, thus allowing for efficient spread of HIV-1 in DC – CD4⁺ T cell co-cultures. These results suggest that immune sensing of HIV-2 in productively infected DCs limits viral spread. Finally, we investigated GM3-expressing nanoparticles (GM3-NPs) for delivery of therapeutics that trigger innate immune responses in CD169⁺ myeloid cells as a novel strategy to mimic myeloid cell-intrinsic virus control observed in HIV-2 infection. We tested the ability of GM3-coated nanoparticles that incorporated a TLR2 ligand, Pam₃CSK₄, to activate CD169⁺ cells. Interestingly, Pam₃CSK₄ containing GM3-NPs robustly activated CD169⁺ cells. These results suggest that induction of dendritic cell-intrinsic type I IFN responses might be a fruitful therapeutic strategy to restrict HIV-1 replication in vivo.