THE GRADUATE COLLEGE OF THE
UNIVERSITY OF OKLAHOMA HEALTH SCIENCES CENTER

ANNOUNCES THE FINAL EXAMINATION OF

# Hem R. Gurung

FOR THE DEFENSE OF THE DOCTOR OF PHILOSOPHY DEGREE
GRADUATE COLLEGE
DEPARTMENT OF MICROBIOLOGY AND IMMUNOLOGY

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Biomedical Research Center, Room 109, 2:00 p.m.

## ROLE OF CORNEAL LYMPHANGIOGENESIS IN RESPONSE TO HERPES SIMPLEX VIRUS TYPE 1 INFECTION

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ABSTRACT: Herpes simplex virus type 1 (HSV-1) remains a highly successful pathogen with a global seroprevalance of more than 60%. Not only is it the casual agent of *herpes labialis* or "cold sore", but it is also the leading cause of infectious corneal blindness in the developed world. Corneal inflammation and neovascularization, a term that encompasses hemangiogenesis and lymphangiogenesis, are evident following HSV-1 infection. The conundrum that exists in such pathology in the mouse is the vessels continue to develop well beyond the resolution of infection. However, the extent to which the newly developed corneal lymphatic vessels impact the generation of cell mediated immunity, and the prognosis of herpetic stromal keratitis (HSK) remain unclear. Here, we show using genetic and molecular techniques in mice that the newly created lymphatic vessels within the cornea in response to HSV-1 infection are functionally capable of draining soluble antigens to the draining lymph nodes, and significantly

impact the clonal expansion of HSV-1-specific CD8+ T cells. Furthermore, we show that migrating corneal dendritic cells do not have significant contribution in this process. Data are also presented that show infiltrating neutrophils are dispensable for corneal neovascularization following resolution of the pathogen. Furthermore, interleukin-6 (IL-6) partially contributes in this process whereas significant suppression of fibroblast growth factor-2 (FGF-2) at the time of virus clearance reverts the cornea to an avascular state. As a measure of ocular function, FGF-2 neutralization preserves visual acuity as measured by optomotor kinetic tracking but does not maintain corneal mechanosensory function. Collectively, the results highlight the significance of HSV-1- induced corneal lymphangiogenesis in adaptive immunity and the pathogenesis of HSK, and identify FGF-2 as the master regulator of corneal neovascularization in a microenvironment that lacks infectious virions in mice.