Bryan A. Johnson

“The activation and consequences of the ATM mediated DNA damage response in HPV infected cells”

Tuesday, April 11, 2017
1:00 p.m.

Joseph S. Pagano Conference Room (00-002)
Lineberger Comprehensive Cancer Center

Dissertation Advisor: Dr. Cary Moody

Presented in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

Reception to follow at 3pm-5pm in LCCC 12-001 (1st floor corner conference room).
ABSTRACT

Bryan Allen Johnson: The activation and consequences of the ATM mediated DNA damage response in HPV infected cells (Under the direction of Cary Moody)

Infection with Human papillomavirus (HPV) is the most prevalent sexually transmitted disease in the world. From a public health standpoint, a subset of mucosa-tropic HPVs termed the high-risk genotypes are of most concern, as they are the causative agents of over 99 percent of cervical cancers and are increasingly linked to other forms of cancer. HPV initially infects the basal keratinocytes of the host epithelium and subsequently undergoes a life cycle tightly linked to the differentiation of its host cell. Despite having a small coding capacity, HPV is a master manipulator of the host cell, subverting a number pathways in order to ensure its own replication. Manipulation of the host cell is largely achieved through the expression of HPV’s two major oncoproteins, E6 and E7, to dysregulate p53 and Rb-E2F signaling respectively.

This dissertation examines the function of the E7 protein in the viral life cycle. E7 expression has been linked previously to the activation of the ATM DNA damage repair pathway throughout infection and the induction of G2 arrest in the upper layers of the stratified epithelium. Here I show that deletion of the Rb binding domain of E7 ablates its ability to increase the levels of ATM pathway proteins in HPV positive cells. Additionally, I demonstrate that E7 broadly upregulates the stability of DNA repair factors to increase their levels, regulating the transcription of only a subset of factors. I also show that the activity of the ATM kinase is necessary to increase the
levels of proteins regulating the G₂/M checkpoint, but does not play a role in increasing the levels of most DNA repair factors. Together, these data establish a model for ATM activation by E7 during HPV infection.