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

CANDIDATE: Samantha Hiemer

DEPARTMENT OR PROGRAM: Biochemistry

TITLE OF DISSERTATION: “Defining Mechanisms Directing Hippo Pathway-Mediated Tumorigenesis”

DATE, TIME, AND PLACE: Thursday, August 27, 2015 at 1:00p.m.
Boston University School of Medicine
72 E. Concord Street, Room K-103
Boston, MA 02118

EXAMINING COMMITTEE

FIRST READER: Dr. Xaralabos Varelas

SECOND READER: Dr. Kathrin Kirsch

THIRD READER:

CHAIRMAN OF THE EXAMINING COMMITTEE: Dr. Matthew Layne
Email: mlayne@bu.edu

ADDITIONAL COMMITTEE MEMBERS: Dr. Valentina Perissi
Dr. Maria Kukuruzinska

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.
DEFINING MECHANISMS DIRECTING HIPPO PATHWAY-MEDIATED TUMORIGENESIS

SAMANTHA E. HIEMER

Boston University School of Medicine, 2016

Major Professor: Xaralabos Varelas, Ph.D., Assistant Professor of Biochemistry

ABSTRACT

Deregulated Hippo pathway signaling promotes the onset of aggressive cancers through the induced nuclear activity of the transcriptional regulators yes-associated protein (YAP) and transcriptional co-activator with PDZ binding motif (TAZ) (YAP/TAZ). Uncontrolled nuclear YAP/TAZ activity evokes tumor-initiating properties in a range of epithelial-derived cancers, but their downstream targets and mechanisms of action are unclear. In particular, recent studies have indicated a role for YAP/TAZ during the progression of oral squamous cell carcinoma (OSCC) and breast cancers. In this thesis I show that YAP/TAZ drive pro-tumorigenic signals in OSCC cells and cooperate with transforming growth factor β (TGFβ) signaling to promote aggressive traits in breast cancer cells. My observations indicated that dysregulated YAP localization precedes OSCC development, and nuclear YAP/TAZ activity drives cell proliferation, survival, and migration in vitro, and is required for tumor growth and metastasis in vivo. Global gene expression studies in OSCC cells revealed that YAP/TAZ-mediated gene expression correlates with gene expression changes that occur in human OSCCs identified by “The Cancer Genome Atlas” (TCGA), many of which encode
regulators of cell cycle progression and survival. TGFβ signaling is known to promote aggressive metastatic properties in late-stage breast cancers but suppresses proliferation in normal epithelial cells and early tumors. However, the mechanism responsible for this switch in TGFβ response is not well defined. My observations suggested that YAP/TAZ are necessary to maintain and promote TGFβ-induced tumorigenic phenotypes in breast cancer and that these phenotypes result from the cooperative activity of YAP/TAZ, the TEA domain family of transcription factors (TEADs), and TGFβ-activated SMAD2/3 in the nucleus. Genome-wide expression analyses indicated that YAP/TAZ, TEADs, and TGFβ-induced signals coordinate a specific pro-tumorigenic transcriptional program. Importantly, genes cooperatively regulated by these complexes, such as the novel targets neuronal growth regulator 1 (NEGR1) and urothelial cancer associated 1 (UCA1), were necessary to maintain tumorigenic activity in metastatic breast cancer cells. Nuclear YAP/TAZ also cooperated with TGFβ signaling to promote phenotypic and transcriptional changes in non-tumorigenic cells to overcome TGFβ-mediated growth inhibition. This work thus defines novel roles for YAP/TAZ in cancer, offering molecular mechanisms that may be useful for identifying and targeting YAP/TAZ-driven cancers.