

University of Maryland Baltimore Graduate School

# Announcement of Doctoral Dissertation Defense\*

Candidate: Petek Ballar

Date, Time, and Place: August 16<sup>th</sup>, 2.00 p.m., HSF II, Room 600

Dissertation Title: Identification of a Novel p97/VCP-interacting motif (VIM) in gp78 and SVIP and its role in the Endoplasmic Reticulum –Associated Degradation (ERAD)

## Dissertation Abstract\*\*:

In eukaryotic cells, 30% of all newly synthesized proteins are estimated to be misfolded or unfolded. Endoplasmic Reticulum-associated degradation (ERAD) is the quality control mechanism that eliminates these unwanted proteins from the ER. Rapid degradation of misfolded proteins restricts delivery of only properly folded proteins to their sites of action. Aberrant ERAD has been implicated in pathogenesis of many diseases, such as cystic fibrosis (CF),  $\alpha$ -1-antitrypsin (AAT) deficiency, diabetes, neurodegenerative diseases, and viral infections. ERAD involves ubiquitination, retrotranslocation from the ER and degradation by the proteasomes in the cytosol. Retrotranslocation requires a subclass of ubiquitin ligases (E3s) that includes gp78 in addition to AAA ATPase p97/VCP and its cofactor, the Ufd1-Npl4 dimer and the putative channel Derlin1. We have previously reported that gp78 interacts directly with p97/VCP. We now identified a novel p97/VCP-interacting motif (VIM) within gp78 and small p97/VCP-interacting protein (SVIP). The VIM of gp78 interacts with the ND1 domain of p97/VCP, the reported binding site of Ufd1, and recruits p97/VCP to the ER without affecting Ufd1 localization. Evaluation of Ufd1's role in gp78-mediated degradation of CD3 $\delta$ , a known substrate of gp78, indicates that gp78-mediated ERAD requires p97/VCP but not Ufd1. Confirmation of presence of a Ufd1-dependent ERAD pathway suggests that gp78 mediates a Ufd1-independent degradation operating in parallel with the previously established p97/VCP-Ufd1-Npl4-mediated mechanism. SVIP, the other VIM containing protein, is anchored to microsomal membranes via myristoylation and localized to the ER. Like gp78, SVIP also physically interacts with p97/VCP and Derlin1. Overexpression of SVIP blocks gp78 association with p97/VCP and Derlin1. This correlates with inhibition of the degradation of both CD3 $\delta$  and the misfolded Z variant of AAT, recently established substrate of gp78. Therefore, SVIP is an endogenous inhibitor of ERAD, acting through regulation of assembly of the gp78-p97/VCP-Derlin1 complex. The mutant cystic fibrosis transmembrane conductance regulator (CFTR $\Delta$ F508), the major cause of CF, is a substrate of gp78-mediated ERAD regulated not only by SVIP but also another ER-membrane E3 hHrd1, which acts as an E3 for gp78. Our work provides important details on the mechanism of ERAD, a prerequisite for the development of strategies to combat many congenital diseases.

Dissertation Committee Chair (name and title):

Bret Hassel, Associate Professor

Dissertation Committee Members (names and titles):

Shengyun Fang, Assistant Professor (supervisor)

Mervyn Monteiro, Professor

Martin Flajnik, Professor

Yun Qiu, Associate Professor

*\*The Open Presentation is open to the university community and invitees of the candidate. Any member of the Graduate Faculty may observe the Final Examination. Only committee members may vote. For more information, see **Procedures for Examination of the Doctoral Dissertation**.*

*\*\*You must type your abstract on this form in the space provided.*

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