

# Announcement of Doctoral Dissertation Defense\*

Candidate: Precious J. Lim

Date, Time, and Place: February 21, 2008, 10 AM, 6<sup>th</sup> fl. Conference Room, UMBI

Dissertation Title: Functional studies of ubiquilin in *Caenorhabditis elegans*:  
Evidence that ubiquilin functions in ER stress response

## Dissertation Abstract\*\*:

Protein quality control in the endoplasmic reticulum (ER) ensures fidelity and proper regulation of protein expression during cell life and differentiation. The accumulation of misfolded and aggregation-prone proteins in the ER activates the unfolded protein response (UPR), which upregulates the expression of ER stress response genes responsible for elimination of such proteins to restore homeostasis. This includes genes involved in ER-associated degradation (ERAD), which retro-translocates terminally misfolded proteins from the ER for degradation in the cytosol. Numerous human diseases are associated with the disruption of the UPR and ERAD, which lead to aggregated misfolded protein deposits that cause cellular dysfunction. We have used *Caenorhabditis elegans* as a model system to demonstrate that ubiquilin is one of the UPR genes upregulated during tunicamycin-induced ER stress and that this upregulation requires the IRE-1 branch of the UPR. We propose that ubiquilin most likely functions in ERAD as loss of ubiquilin by RNA interference (RNAi) resulted in an increased accumulation of polyubiquitinated proteins, which ultimately led to a shortened lifespan. This was recapitulated in a mutant strain that contained a deletion in the ubiquilin gene thereby generating a loss-of-function protein. Moreover, we show through RNAi experiments that ubiquilin modulates the expression and processing of a protein known to function in ERAD. We also demonstrate the involvement of ubiquilin in an animal model of Huntington's disease. We show that overexpression of mRFP-tagged ubiquilin prevented and rescued a motility defect caused by expression of the human huntingtin exon 1 fragment containing toxic polyglutamine tracts while loss of ubiquilin by RNAi and genetic deletion experiments exacerbated this defect. Our results strongly support a role for ubiquilin as a key component in the ER stress response to maintain protein homeostasis. Methods to regulate expression of ubiquilin may provide a therapeutic strategy to a variety of diseases caused by protein misfolding.

Dissertation Committee Chair: Mervyn J. Monteiro, Ph.D. Professor

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