

University of Maryland Baltimore Graduate School

# Announcement of Doctoral Dissertation Defense\*

Candidate: Guanjun Xia

Date, Time, and Place: 02/25/2008, 2:00 P.M., Pharmacy Learning Center (PLC – 110 N Pine St) Room 107

Dissertation Title: Novel Role of Lymphocyte-Specific Kinase (Lck) and Filamin A (FLNA) in Activation-Induced T Cell Synapse Formation and the Characterization of Novel Small Molecule Inhibitors Targeting Lck SH2 Domain

## Dissertation Abstract\*\*:

Lck is a Src family non-receptor kinase preferentially expressed in T cells. Lck phosphorylates tyrosine residues of immunoreceptor tyrosine based activation motif (ITAM) present in the cytoplasmic domains of CD3 complex upon T cell receptor (TCR) activation. These phosphotyrosine residues provide docking sites for selective signaling molecules. Concurrent to the TCR proximal signaling events, all of the TCR expressed uniformly on cell surface will assemble at the interface of antigen presenting cell (APC) and T cell and form immunologic synapse (IS). IS formation is an integral part of T cell activation process without which down stream signaling process will not take place. The molecular mechanism of IS formation is currently not understood.

Results from studies presented in this thesis point to an intriguing molecular mechanism responsible for the formation of activation-induced immunologic synapse, a critical phase in T cell activation process. Experimental results from yeast two hybrid analyses, dominant negative constructs, and immunoprecipitation indicate that Lck constitutively associates with Filamin A (FLNA) with its SH3 domain and recruits FLNA in an activation-dependent manner to associate with CD3  $\zeta$  chain. In activated T cells, the SH2 domain of Lck binds to the phosphorylated CD3 ITAMs thereby facilitating TCR/CD3/FLNA association. The dimeric nature of FLNA together with multiple ITAMs in CD3 chains promote the oligomerization/clustering of TCR/CD3 in activated T cells. Lck functions as molecular glue in this process. Based on this finding, it was anticipated that the disruption of Lck SH2 domain binding to the CD3 ITAM in activated T cells might lead to the inhibition of receptor oligomerization and/or T cell activation. Taking advantage of the available crystal structure of Lck SH2 domain, specific small molecule inhibitors capable of blocking Lck SH2 binding to the  $\zeta$  chain ITAM were identified utilizing computer aided drug design (CADD) approach. Three small molecule inhibitors of Lck SH2 domain (SMILS) were identified and tested for their function *in vitro* and *in vivo*. These SMILS compounds inhibited T cell activation and prevented progression of adjuvant arthritis (AA) in rats.

Dissertation Committee Chair (name and title):

Paul Shapiro, Ph.D., Associate Professor

Dissertation Committee Members (names and titles):

Jun Hayashi, Ph.D., Associate Professor

Natalie Eddington, Ph.D., Professor, Dean

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*\*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.*

Updated: February 24, 2006