

University of Maryland Baltimore Graduate School

Announcement of Doctoral Dissertation Defense*

Candidate: Panomwat Amornphimoltham

Date, Time, and Place: August 23, 2007 *Dental School - 1:00pm - 4:00pm*

Dissertation Title: mTOR, a therapeutic target in head and neck squamous cell carcinoma

Dissertation Abstract**:

Squamous cell carcinoma of the head and neck (HNSCC) is the 6th most common cancer in the developed world, affecting nearly 44,000 patients and resulting in ~11,000 deaths each year in the US alone. Despite significant advance in conventional therapies, the survival rate of HNSCC patients had merely improved over the past three decades, reflecting the urgent need for the development of novel and more effective treatment strategies. A better understanding of the mechanism involved in tumorigenesis has afforded the opportunity to initiate new molecular targeting strategies for cancer treatment. In this regard, we observed that persistent activation of the Akt pathway is a frequent event in HNSCC. Akt promotes cell proliferation by coordinating mitogenic signaling with energy and nutrient-sensing pathways controlling protein synthesis through the mammalian target of rapamycin (mTOR). These findings prompted us to investigate the consequences of interfering with mTOR function in HNSCC. We found that rapamycin rapidly reduced the elevated levels of phospho-S6, a downstream mTOR effector, in HNSCC cells *in vitro* and displayed a potent anti-tumoral effect in HNSCC xenografts *in vivo*. However, rapamycin did not affect HNSCC cells growth *in vitro*, raising the possibility that, as for other cancers, rapamycin may not target cancer cells directly but may instead act based on its anti-angiogenic properties. To address this issue, we have utilized a retro-inhibition approach consisting in the expression of a rapamycin-resistant mTOR mutant in HNSCC cells, while retaining wild-type mTOR in host-derived stromal cells, which hence remained rapamycin-sensitive. This reverse-pharmacology strategy revealed that HNSCC cells are the primary target of HNSCC *in vivo*, and enabled monitoring the direct consequences of inhibiting mTOR within the complex tumor microenvironment. We also used the well-established two-step chemical carcinogenesis mouse model to explore the effectiveness of rapamycin in HNSCC using an animal model reflecting better the complexity of the clinical setting. Rapamycin administration caused a dramatic decrease in the tumor burden, and prolonged the survival of tumor-bearing mice. Collectively, these findings define the Akt-mTOR pathway as a therapeutic target for HNSCC, thus raising the possibility of exploring the clinical activity of rapamycin in HNSCC patients.

Dissertation Committee Chair (name and title): Dr. John J Sauk

Dissertation Committee Members (names and titles):

Dr. Silvio J Gutkind

Dr. Bernard A. Levy

Dr. Anne W. Hamburger

Dr. John R. Basile

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